Autoinflammatory disease, multisystem, with immune dysregulation, X-linked (ADMIDX, MONDO:0957494, OMIM:301109)

Summary

ADMIDX is caused by hemizygous loss-of-function variants in **DOCK11** (HGNC:23483, Xq24, gene OMIM 300681, UniProt Q5JSL3), a 2073-amino-acid atypical guanine nucleotide exchange factor (GEF) that loads GTP onto the Rho GTPase CDC42. The disease is an X-linked recessive inborn error of immunity, one of the "actinopathies" in which a defect in an actin-cytoskeleton regulator produces combined immunodeficiency, autoinflammation and autoimmunity. Thirteen affected males from 12 families have been published between 2023 and 2025 (PMID: 36952639, PMID: 37342957, PMID: 40274249), plus isolated later reports. They present in infancy or childhood with autoimmune cytopenias, normocytic anaemia with anisopoikilocytosis, inflammatory bowel disease, benign lymphoproliferation, systemic inflammation, skin disease and recurrent infection.

Three results from this investigation go beyond assembling the published descriptions. First, four 2026 cryo-EM structures of full-length DOCK11 (PDB 22VD, 22VE, 22VF, 22VG; PMID: 42837459) show that DOCK11 works as a thresholded switch with positive feedback: CDC42-GTP binds a distal armadillo-repeat site, which drives DOCK11 to the plasma membrane and raises exchange activity at the catalytic DOCKER domain. Output is therefore not proportional to DOCK11 protein level, which explains why hypomorphic missense alleles that merely reduce protein cause disease as severe as null alleles. Second, the apparent conflict between fully penetrant X-linked disease and 59 hemizygous male pLoF observations in gnomAD v4 resolves by position: the 23 pLoF alleles actually seen in a hemizygous male truncate at median codon 921 of 2073 (44% of the open reading frame) whereas the five reported disease truncating alleles truncate at median codon 1464 (71%), Mann-Whitney U = 21, p = 0.0137, rank-biserial = −0.635, with only 3/23 (13%) of the hemizygote-observed alleles at or after the DOCKER domain start at codon 1609. Third, the hypothesis that immune-restricted disease reflects immune-restricted expression is refuted: GTEx v8 puts DOCK11 highest in subcutaneous adipose (45.4 TPM) and tibial artery (31.9 TPM), above spleen (21.2 TPM), and the Human Protein Atlas classifies it as "Low tissue specificity, Detected in all".

Allele class splits the clinical picture. Variants that abolish DOCK11 protein associate with autoinflammation and recurrent pneumonia; missense variants that reduce protein associate with autoantibody-driven autoimmunity (Fisher exact p = 0.035 on 5 null versus 8 missense patients, with a zero cell, so the odds ratio is uninformative and the p value should be read as suggestive). Allogeneic haematopoietic stem cell transplantation is the only curative treatment reported (PMID: 39644982). Its mechanistic rationale is exactly the expression result above: DOCK11 is expressed everywhere yet disease is confined to the haematopoietic compartment, so replacing that compartment should correct the phenotype in full. Every frequency and effect size in this report rests on 1 to 13 patients, which is the dominant limitation throughout.

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1. Disease information

ADMIDX is a monogenic, X-linked recessive inborn error of immunity that combines immune dysregulation (autoimmune cytopenias, lupus-like autoimmunity, inflammatory bowel disease), autoinflammation (fever, serositis, panniculitis, elevated proinflammatory cytokines), a variable primary immunodeficiency (recurrent pneumonia, bronchiectasis, BCGitis, low IgA) and a haematological phenotype dominated by normocytic anaemia with abnormal red cell morphology. Onset is typically in infancy or early childhood.

Resource	Identifier
MONDO	MONDO:0957494
OMIM (phenotype)	OMIM:301109
OMIM (gene, DOCK11)	300681
HGNC	HGNC:23483
NCBI Gene	139818
Ensembl	ENSG00000147251
UniProt	Q5JSL3
UniProt disease entry	DI-06712
Canonical transcript	ENST00000276202 / NM_144658.4
Cytogenetic location	Xq24, GRCh38 chrX:118,495,612-118,686,976 (+ strand)
Orphanet	No dedicated ORPHA code identified for ADMIDX as of this review
ICD-10	No specific code. D84.8 (other specified immunodeficiency disorders) is the closest available
ICD-11	No specific code. 4A00.Z or 4A01.Z (immunodeficiency, unspecified) is the closest available
MeSH	No dedicated descriptor identified

Synonyms: DOCK11 deficiency; X-linked multisystem autoinflammatory disease with immune dysregulation; X-linked actinopathy with autoimmunity; ADMIDX.

Information source type. All phenotype frequencies here derive from aggregated disease-level curation (HPO annotations of OMIM:301109) built from published individual case series. No EHR-derived cohort, registry or natural history study exists for this disease. The 50 HPO annotations have denominators of 1 to 12 patients.

2. Etiology

Disease causal factors

The cause is monogenic and genetic: hemizygous pathogenic variants in DOCK11 in males. No environmental, infectious or toxic cause contributes to disease occurrence. Two mutational mechanisms are documented in the index cohorts.

> "We identified rare, X-linked germline mutations in DOCK11 in the patients, leading to a loss of protein expression in two patients and impaired CDC42 activation in all four patients." (PMID: 37342957, human clinical plus in vitro)
>
> "We studied 8 male patients, from 7 unrelated families, with hemizygous DOCK11 missense variants leading to reduced DOCK11 expression." (PMID: 36952639, human clinical)

Genetic risk factors

The DOCK11 variant itself is the sole established genetic risk factor. gnomAD v4 constraint metrics show the gene is depleted of both classes of damaging variation in population controls: observed/expected LoF = 0.414 (LOEUF 0.505, lof_z 6.46) and observed/expected missense = 0.758 (mis_z 4.05), against syn_z 0.32. The pLI of 0.103 is low, as expected for an X-linked gene where hemizygous pLoF alleles are still observed in males; it does not argue against pathogenicity.

Male sex is a risk factor in the trivial X-linked sense: all 13 reported patients are male. Family history of an affected maternal male relative is a risk factor for a carrier mother's sons (50% per male pregnancy).

Environmental risk factors

✖ None identified. No toxin, occupational exposure, diet, radiation or lifestyle factor has been associated with ADMIDX occurrence. The disease is fully genetically determined given a hemizygous pathogenic allele.

Protective factors

? No genetic modifier or protective allele has been identified. The gnomAD positional analysis in section 4 suggests, as an inference and not a demonstrated protective mechanism, that truncations in the first half of the open reading frame are tolerated in hemizygous males while truncations at or near the DOCKER domain are not. Whether a clean null allele is milder than a DOCKER-truncating allele is an open and testable question.

Environmental protective factors are not applicable to disease occurrence. For disease course, antibiotic prophylaxis and immunoglobulin replacement reduce infection burden (section 12), and avoidance of live vaccines including BCG prevents vaccine-strain disease (section 13).

Gene-environment interactions

One interaction is documented in principle: live attenuated BCG vaccination in a DOCK11-deficient infant can produce BCGitis (HP:0020086, annotated 1/4). A separate report of disseminated BCG infection in a Beijing infant lists multiple gene defects including exon 13 of DOCK11 alongside CR2, IFNAR2 and TLR2, so that case does not establish DOCK11 as the sole cause (PMID: 40811145, human clinical). Infection as a trigger for hyperinflammatory episodes is reported in the nonsense-variant patient, who had "infection-triggered hyperinflammation" (PMID: 40274249).

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3. Phenotypes

All 50 HPO terms annotated to OMIM:301109 were retrieved programmatically from the HPO annotation API with per-term frequencies and source PMIDs. Denominators are 2, 4, 5, 8 or 12, so Wilson 95% confidence intervals are wide throughout.

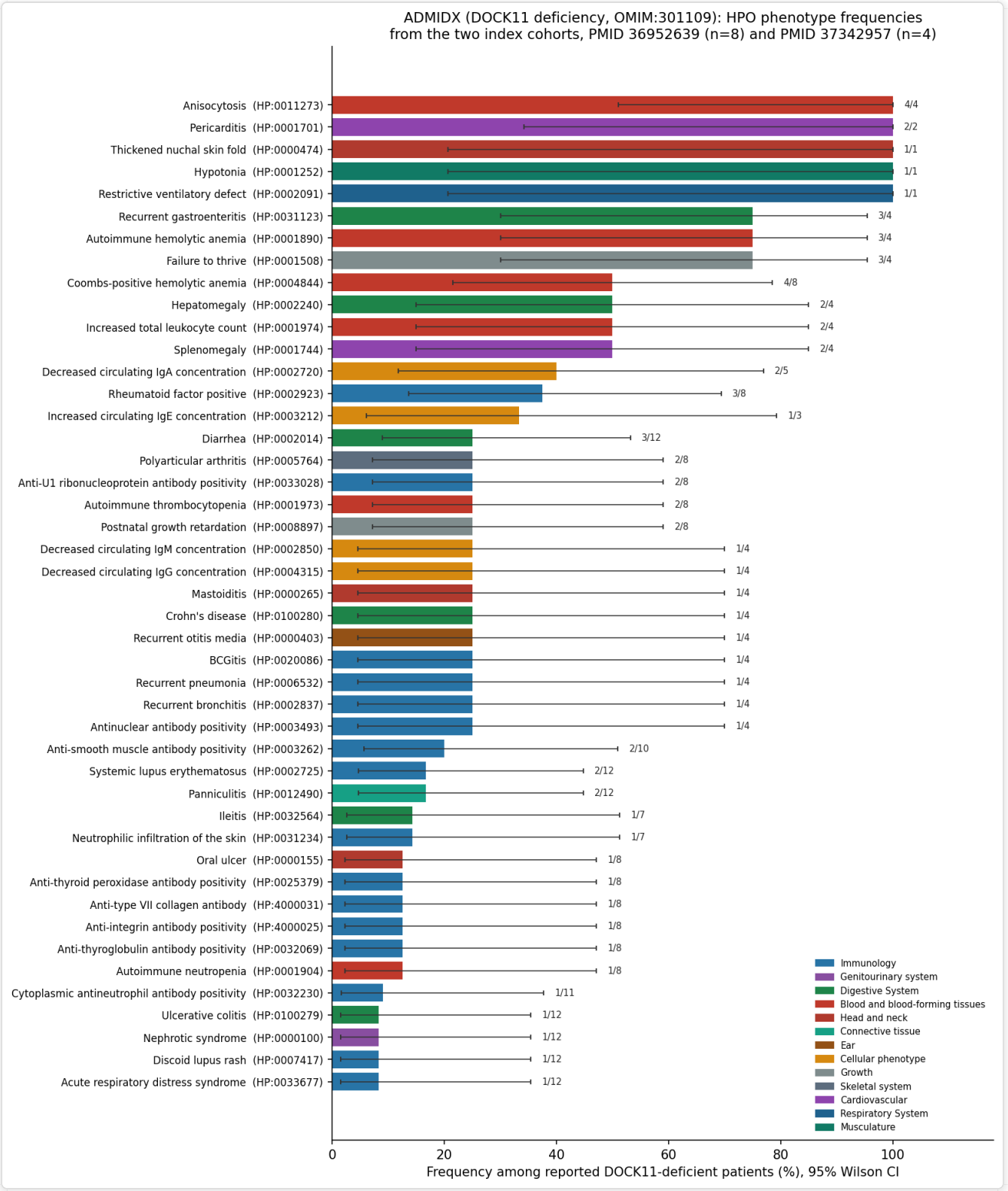


Figure 1. *Phenotype frequency spectrum of DOCK11 deficiency from the 50 HPO annotations of OMIM:301109, with Wilson 95% confidence intervals. Denominators range from 2 to 12 patients, so all intervals are wide.*

Haematological phenotypes (laboratory abnormalities and clinical signs)

Phenotype	HPO	Frequency (k/n)	Wilson 95% CI
Anisocytosis / anisopoikilocytosis	HP:0011273	4/4 (100%)	51-100%
Autoimmune haemolytic anaemia	HP:0001890	3/4 (75%)	30-95%
Coombs-positive haemolytic anaemia	HP:0004844	4/8 (50%)	22-78%
Increased total leukocyte count	HP:0001974	2/4 (50%)	wide
Autoimmune thrombocytopenia	HP:0001973	2/8 (25%)	wide
Autoimmune neutropenia	HP:0001904	1/8 (13%)	wide

Anisocytosis at 4/4 is the single most frequent annotation. The Wilson lower bound of 51% means the data cannot distinguish a universal feature from a merely common one. Anaemia is normocytic and of variable severity. Phenotype type: laboratory abnormality for the cell counts and film morphology (LOINC equivalents exist for haemoglobin, red cell distribution width and the direct antiglobulin test), clinical sign for the pallor and jaundice of haemolysis.

Autoimmune and autoinflammatory phenotypes

Phenotype	HPO	Frequency (k/n)
Pericarditis	HP:0001701	2/2
Rheumatoid factor positive	HP:0002923	3/8
Anti-U1 RNP antibody positivity	HP:0033028	2/8
Polyarticular arthritis	HP:0005764	2/8
Systemic lupus erythematosus	HP:0002725	2/12
Panniculitis	HP:0012490	2/12
Discoid lupus	HP:0007417	1/12
Nephrotic syndrome	HP:0000100	1/12

Gastrointestinal and hepatosplenic phenotypes

Phenotype	HPO	Frequency (k/n)
Recurrent gastroenteritis	HP:0031123	3/4
Diarrhoea	HP:0002014	3/12
Splenomegaly	HP:0001744	2/4
Hepatomegaly	HP:0002240	2/4
Crohn disease	HP:0100280	1/4
Ulcerative colitis	HP:0100279	1/12

Acute liver failure is reported as a presenting feature in a separate case (PMID: 40107756).

Infection, immunodeficiency and growth phenotypes

Phenotype	HPO	Frequency (k/n)
Failure to thrive	HP:0001508	3/4
Decreased circulating IgA	HP:0002720	2/5
Postnatal growth retardation	HP:0008897	2/8
BCGitis	HP:0020086	1/4
Recurrent pneumonia	HP:0006532	1/4

Developmental delay is reported in the four-patient series. Bronchiectasis is reported in the nonsense-variant patient. Recurrent febrile episodes and seizures are reported in a 10-year-old (PMID: 41250716).

Onset, severity, progression

Onset annotations: juvenile 6/8, childhood 3/12, infantile 2/4, congenital 1/4. Inheritance is annotated X-linked recessive (HP:0001419). Severity is variable and spans a 10-year-old boy managed by "watchful waiting" (PMID: 41250716) to death in childhood recorded in UniProt DI-06712. The autoinflammatory component is episodic (recurrent febrile episodes), while cytopenias and gut disease are chronic with relapses.

Quality of life

⚠ No EQ-5D, SF-36, PROMIS or disease-specific quality-of-life instrument has been applied to any ADMIDX patient. Per-phenotype impact can only be inferred: failure to thrive and postnatal growth retardation (3/4 and 2/8) imply chronic nutritional and developmental burden; transfusion-dependent or immunosuppression-dependent haemolytic anaemia, chronic colitis and recurrent hospitalisation for febrile episodes imply high care intensity; developmental delay implies educational support needs. These are inferences from the phenotype list, not measured outcomes.

4. Genetic and molecular information

Causal gene

DOCK11 (aliases ZIZ2, Zizimin-2, ACG, ADMIDX), HGNC:23483, NCBI Gene 139818, gene OMIM 300681. The protein is 2073 aa, 237.7 kDa, named in UniProt as "Activated Cdc42-associated guanine nucleotide exchange factor" and Zizimin-2. It belongs to the DOCK-D subfamily with DOCK9 and DOCK10. GTPase specificity is narrow:

> "Zizimin2 and zizimin1 have similar primary structures and both proteins bound and activated Cdc42 but not the Cdc42-related proteins TC10 or TCL." (PMID: 15710388, in vitro)

Domain architecture and variant positions

Domain	Residues	Function
PH	165-272	Membrane contact
C2 DOCK-type (DHR-1)	640-818	Phosphoinositide-dependent membrane targeting
Disordered region	1226-1267	Not assigned
Armadillo repeats	mid-protein, distal CDC42-GTP site	Positive feedback site, defined by cryo-EM
DOCKER (DHR-2)	1609-2036	Catalytic GEF; binds activated CDC42 together with residues 66-126

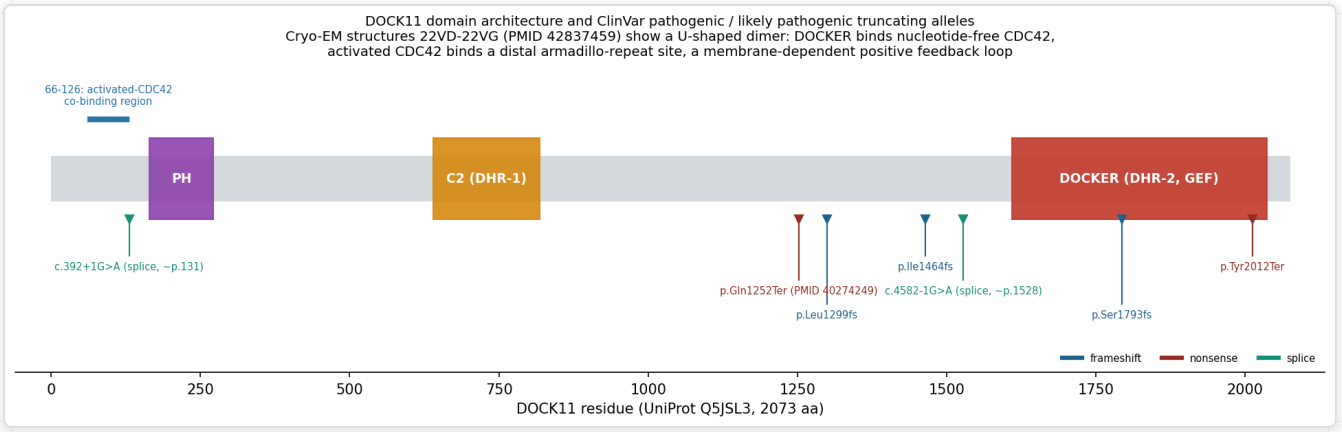


Figure 2. *DOCK11 domain map (PH 165-272, C2/DHR-1 640-818, DOCKER/DHR-2 1609-2036) with the positions of the seven ClinVar pathogenic and likely pathogenic DOCK11-specific truncating and splice alleles. Every one removes or disrupts the catalytic DOCKER domain.*

Pathogenic variants

ClinVar holds 600 summarised DOCK11 records: 14 Pathogenic, 6 Likely pathogenic, 173 VUS, 14 Likely benign, 1 Benign, 3 Conflicting and 389 unclassified. Variant types: 576 SNV, 9 copy-number gain, 7 copy-number loss, 3 microsatellite, 2 duplication, 2 deletion, 1 complex. Only 7 of the 20 P/LP records are DOCK11-specific small variants; the remaining 13 are large Xq copy-number events spanning DOCK11 and classified for other reasons (Klinefelter syndrome, Menkes disease).

Variant (NM_144658.4)	Protein	Class	Classification
c.392+1G>A	splice donor, ~p.131	Splice-site	Pathogenic
c.3754C>T	p.(Gln1252Ter)	Nonsense	Reported pathogenic (PMID: 40274249)
c.3895_3896del	p.Leu1299fs	Frameshift	Pathogenic
c.4389dup	p.Ile1464fs	Frameshift	Pathogenic
c.4582-1G>A	splice acceptor, ~p.1528	Splice-site	Pathogenic
c.5377_5378del	p.Ser1793fs	Frameshift	Pathogenic
c.6036C>A	p.Tyr2012Ter	Nonsense	Pathogenic

All seven truncate at or before the end of the DOCKER domain, so all remove or disable catalytic GEF activity. The eight disease-causing missense alleles from PMID: 36952639 are not deposited with P/LP status, so a clinical laboratory encountering a DOCK11 missense variant today will usually return a VUS. That makes functional confirmation by CDC42-GTP loading or a filopodium assay part of the diagnostic path. A published neonatal case demonstrates the value of negative functional testing for a DOCK11 VUS (PMID: 42382659).

Allele frequency in population databases

gnomAD v4 (730,947 exomes plus 76,215 genomes) contains 365 LOFTEE high-confidence pLoF DOCK11 variants, 139 passing all filters, 281 total pLoF alleles and 59 hemizygous male observations. Cumulative pLoF allele frequency is 2.581×10^{-4}, giving a crude upper-bound male carrier frequency of 1.48×10^{-4}, about 1 in 6,780 males. That upper bound is far above the observed case count, and the positional analysis below explains why.

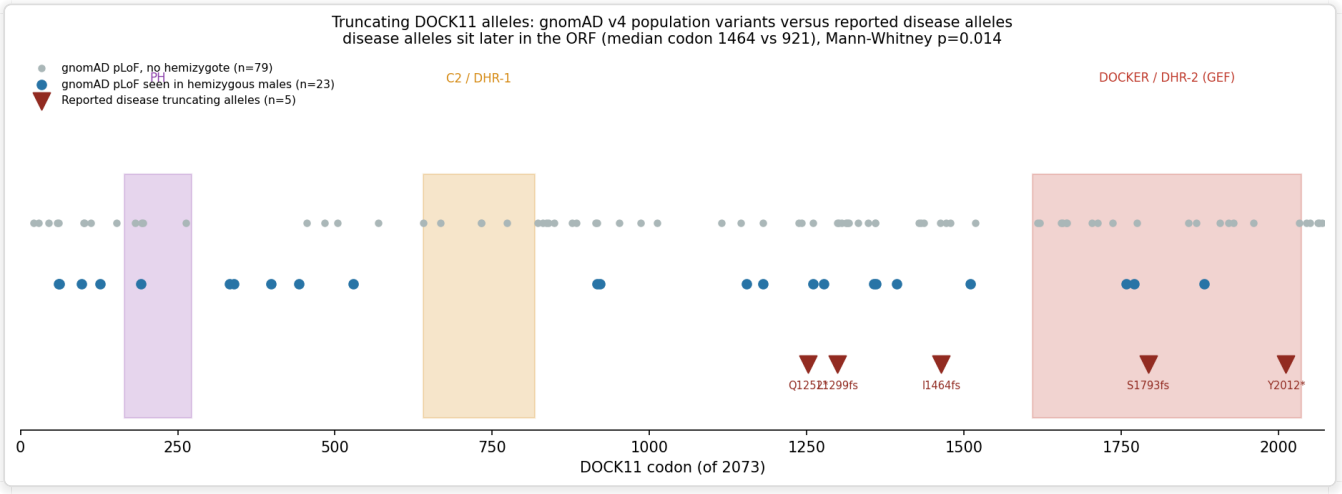


Figure 3. *Positional comparison of gnomAD v4 pLoF alleles against reported disease-causing DOCK11 truncating alleles, with the derived prevalence upper bound. The 23 pLoF alleles observed in hemizygous males truncate at median codon 921 of 2073 against median codon 1464 for the five disease alleles (Mann-Whitney p = 0.0137).*

Of the 139 PASS high-confidence pLoF variants, 102 have a parseable protein position. The 23 observed in a hemizygous male have median codon 921 (44% of the ORF); the five reported disease truncating alleles have median codon 1464 (71%). Mann-Whitney U = 21, p = 0.0137, rank-biserial = −0.635. Only 3/23 (13%) of the hemizygote-observed alleles fall at or after the DOCKER start at codon 1609.

Two reconciling explanations fit. Early truncations are the ones tolerated in hemizygous males, consistent with efficient nonsense-mediated decay plus use of a downstream alternative start, or with LOFTEE misannotation in exons that are not constitutively included. Disease alleles cluster in the C-terminal half, where a stable truncated protein retaining the PH and C2/DHR-1 membrane-contact modules can still localise to the

membrane but cannot catalyse exchange, acting as a dead-end CDC42 scaffold. This predicts a clean null allele may be milder than the reported disease alleles. The prediction is testable by expressing the patient truncations and measuring CDC42-GTP loading. gnomAD also depletes severe paediatric disease, which independently enriches population carriers for benign-end alleles.

Somatic versus germline origin

All reported disease variants are germline. No somatic DOCK11 variant causing ADMIDX has been described, and COSMIC somatic DOCK11 entries relate to tumour biology, not to this disease. Germline mosaicism has not been reported for DOCK11; it cannot be excluded on 12 families.

Functional consequence

Loss of function, by two routes. Truncating and splice alleles remove the catalytic DOCKER domain. Missense alleles reduce steady-state protein ("hemizygous DOCK11 missense variants leading to reduced DOCK11 expression", PMID: 36952639), a hypomorphic mechanism. No gain-of-function allele is reported in patients, although the dead-end-scaffold model above is formally a dominant-negative-like mechanism operating within a hemizygous cell.

Modifier genes, epigenetics, chromosomal abnormalities

? No modifier gene has been identified for ADMIDX. One child with paediatric autoimmune cytopenia and inflammatory bowel disease carried a DOCK11 germline variant among three genetically explained cases out of ten tested (PMID: 39155467), which places DOCK11 in the differential for that combination but gives no modifier information.

No disease-specific DNA methylation or histone modification signature has been reported for ADMIDX. DOCK11 does influence chromatin association in a different context: in hepatocytes it facilitates the association of hepatitis B covalently closed circular DNA with H3K4me3 and RNA Pol II while playing limited direct part in histone modification itself (PMID: 37243264, in vitro). That is virology, not ADMIDX pathogenesis.

Large Xq copy-number changes spanning DOCK11 exist in ClinVar but are classified for other contiguous-gene reasons. No ADMIDX case is attributed to a chromosomal rearrangement.

5. Environmental information

Environmental factors. No toxin, radiation, pollutant or occupational exposure is implicated in ADMIDX causation. CTD and toxicogenomic sources return no DOCK11 environmental association relevant to this phenotype.

Lifestyle factors. Not applicable to disease occurrence. Smoking, diet, exercise and alcohol have no established relationship to ADMIDX onset or severity.

Infectious agents. Pathogens do not cause ADMIDX but act as triggers and complications. Mycobacterium bovis BCG (vaccine strain, NCBITaxon:33892) can cause BCGitis in affected infants (HP:0020086, 1/4). Recurrent bacterial pneumonia with progression to bronchiectasis occurs with expression-null alleles. Recurrent gastroenteritis is annotated 3/4. Infection-triggered hyperinflammation is documented (PMID: 40274249). A separate DOCK11 biology, as a hepatitis B host factor required for covalently closed circular DNA maintenance (PMID: 36270602, PMID: 38793626, PMID: 42300748), is unrelated to ADMIDX pathogenesis but is relevant to any future DOCK11-directed therapeutic.

6. Mechanism and pathophysiology

Causal chain

1. A hemizygous DOCK11 variant on the single male X chromosome **leads to** either loss of DOCK11 protein (truncating, splice or nonsense alleles at codons 1252-2012) or reduced steady-state DOCK11 protein (missense alleles). *Demonstrated in patient cells, PMID: 37342957, PMID: 36952639.*
2. Loss or reduction of DOCK11 **results in** failure of the DOCKER (DHR-2) domain to catalyse GDP-to-GTP exchange on CDC42 at the plasma membrane. *Demonstrated: impaired CDC42 activation in all four patients, PMID: 37342957.*
3. Failed exchange **prevents** the positive-feedback step in which CDC42-GTP binds the distal armadillo-repeat site, recruits DOCK11 to the membrane and raises the exchange rate, so local CDC42-GTP never reaches threshold. *Demonstrated structurally and biochemically for wild-type DOCK11, PMID: 42837459. That patient alleles specifically break this loop is inferred from variant position mapped onto the structures.*
4. Sub-threshold CDC42-GTP **leads to** failure of CDC42-dependent actin nucleation, so filopodia do not form, the immune synapse does not assemble normally and cells cannot migrate through confined channels. *Demonstrated for filopodia in mouse dendritic cells, PMID: 22494997; conserved in C. elegans neurite branching through cdc-42 and toca-1, PMID: 41278672.*

5. Loss of cytoskeletal control **results in** altered signalling thresholds at the T cell receptor, because actin architecture sets receptor clustering and sustained signalling. *Inferred from actinopathy biology; the downstream readout in step 6 is demonstrated.*

Branch A, autoinflammation:

1. Altered T cell signalling **leads to** overt T cell activation with increased nuclear translocation of NFATc1 and output of proinflammatory cytokines. *Demonstrated in patient T cells and Dock11-knockout mouse T cells, PMID: 37342957.*
2. Sustained cytokine output **results in** systemic autoinflammation: recurrent fever, serositis including pericarditis (2/2), panniculitis (2/12), leukocytosis (2/4), hepatosplenomegaly (2/4 each).

Branch B, autoantibody autoimmunity:

1. Reduced DOCK11 **leads to** an abnormal regulatory T cell phenotype with profoundly reduced FOXP3 and IKZF2 and impaired IL-2 to STAT5B signalling. *Demonstrated, PMID: 36952639.*
2. Loss of Treg identity **results in** unrestrained autoreactive B cell help, which **produces** rheumatoid factor (3/8), anti-U1 RNP (2/8), Coombs-positive haemolytic anaemia (4/8), autoimmune thrombocytopenia (2/8), systemic lupus erythematosus (2/12), discoid lupus and nephrotic syndrome.

Branch C, humoral defect:

1. Loss of DOCK11 in B cells **leads to** reduced marginal zone B cell formation and impaired secondary humoral responses. *Demonstrated in mouse, PMID: 25729399, PMID: 34980182.* This **results in** low IgA (2/5), recurrent sinopulmonary infection and, with chronic infection, bronchiectasis.

Branch D, myeloid defect and infection:

1. Loss of CDC42-driven filopodia in macrophages **results in** impaired macrophage chemotaxis, which **leads to** recurrent pneumonia, recurrent gastroenteritis (3/4) and failure to control live BCG (1/4). *Macrophage chemotaxis demonstrated in the Dock11-tm1Thar mouse.*

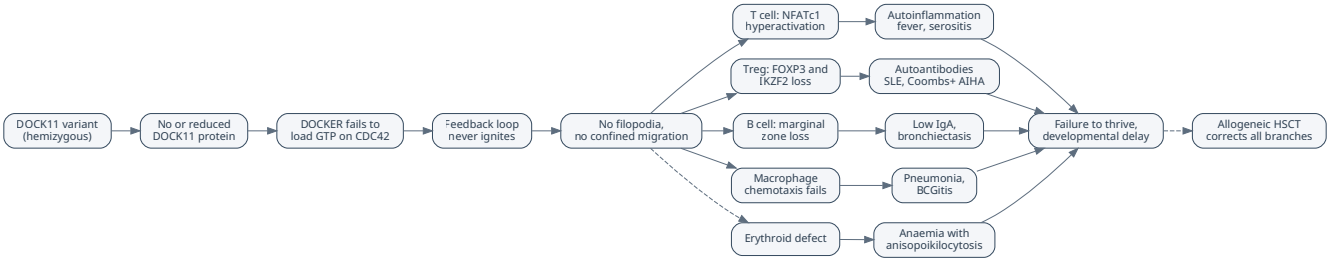
Branch E, erythroid and platelet involvement:

1. Loss of DOCK11 in the erythroid lineage **results in** normocytic anaemia with anisopoikilocytosis (4/4). *Demonstrated by recapitulation in a dock11-knockout zebrafish, PMID: 37342957. The cell-intrinsic mechanism in human erythroblasts is not established.*

Convergence and therapeutic consequence:

1. Chronic inflammation from branches A to E **leads to** failure to thrive (3/4), postnatal growth retardation (2/8) and developmental delay.

2. Because DOCK11 is expressed in all human tissues yet disease is confined to blood cells, replacement of the haematopoietic compartment **is predicted to** correct the entire phenotype, which is the mechanistic justification for allogeneic HSCT. *Inferred from expression data plus the clinical practice reported for this disease group, PMID: 39644982.*



Molecular pathways

Rho GTPase signalling through CDC42 (KEGG hsa04810 regulation of actin cytoskeleton; Reactome Rho GTPase cycle and CDC42 GTPase cycle). Downstream of CDC42-GTP: WASP to Arp2/3 actin nucleation, formin-driven filopodial elongation, PAK kinases. In T cells the failure propagates to the calcium-calcineurin-NFAT axis, read out as increased NFATc1 nuclear translocation. In regulatory T cells it propagates to IL-2 receptor to STAT5B, read out as reduced FOXP3 and IKZF2.

Protein dysfunction, from structure

Four cryo-EM structures of full-length human DOCK11 were released 2026-10-21: PDB **22VD** (apo dimer, 3.80 Å), **22VE** (with nucleotide-free Cdc42 G15A, 4.28 Å), **22VF** (ternary, with Cdc42 G15A plus Cdc42 Q61L-GTP, 3.82 Å) and **22VG** (membrane-bound ternary complex, 6.07 Å), all from PMID: 42837459.

> "DOCK11 predominantly adopts a U-shaped dimer that binds to nucleotide-free Cdc42 via the catalytic domain, whereas activated Cdc42 engages a distal site within the armadillo-repeat domain." (structural)
>
> "binding of activated Cdc42 is critical for enhancing the membrane-dependent nucleotide exchange activity of DOCK11, promoting its localization to the plasma membrane, and facilitating intracellular activation of Cdc42" (structural, biochemical and cellular)

The membrane-bound ternary complex adopts an extended conformation that aligns multiple membrane-contact elements. 💡 This makes DOCK11 a switch with gain. Below a threshold the feedback loop does not ignite at all, which is the mechanistic reason a missense allele that merely halves protein produces disease as severe as a null.

Cellular processes and GO terms

GO term	ID	Aspect
Guanyl-nucleotide exchange factor activity	GO:0005085	MF
Small GTPase binding	GO:0031267	MF
Positive regulation of GTPase activity	GO:0043547	BP
Positive regulation of filopodium assembly	GO:0051491	BP (IMP)
Regulation of Rho protein signal transduction	GO:0035023	BP
Marginal zone B cell differentiation	GO:0002315	BP
B cell homeostasis	GO:0001782	BP
Cytosol	GO:0005829	CC

Additional biological processes relevant to the causal chain: actin filament polymerization (GO:0030041), immunological synapse formation (GO:0001771), leukocyte migration (GO:0050900), regulatory T cell differentiation (GO:0045066), positive regulation of T cell activation (GO:0050870), erythrocyte differentiation (GO:0030218).

Cell types (CL terms)

Cell type	CL	Evidence
T cell	CL:0000084	NFATc1 hyperactivation, cytokine output (PMID: 37342957)
Regulatory T cell	CL:0000815	Reduced FOXP3 and IKZF2 (PMID: 36952639)
Marginal zone B cell	CL:0000844	Reduced number in mouse (PMID: 25729399)
B cell	CL:0000236	Impaired secondary humoral response (PMID: 34980182)
Macrophage	CL:0000235	Impaired chemotaxis (mouse Dock11-tm1Thar)
Dendritic cell	CL:0000451	Filopodia induction (PMID: 22494997)
Erythrocyte	CL:0000232	Anisopoikilocytosis (PMID: 37342957)
Haematopoietic stem cell	CL:0000037	DOCK11-CDC42 axis sets HSC polarity (PMID: 40643159)
Platelet	CL:0000233	Thrombocytopenia

Metabolic and biochemical abnormalities

No metabolomic, lipidomic or enzyme-deficiency signature has been reported for ADMIDX. The biochemical defect is specific: failure of guanine nucleotide exchange on CDC42. Relevant CHEBI entities are GTP (CHEBI:15996), GDP (CHEBI:17552) and the phosphoinositides that direct DOCK11 membrane contact, phosphatidylinositol 3,4,5-trisphosphate (CHEBI:16618) and phosphatidylinositol 4,5-bisphosphate (CHEBI:18348).

Tissue damage mechanisms

Tissue injury is immune-mediated rather than metabolic or ischaemic. Red cells are destroyed by autoantibody-mediated haemolysis (Coombs-positive, 4/8). Gut mucosa is injured by chronic lymphocytic and granulomatous inflammation. Airways are damaged by repeated bacterial infection, producing fixed bronchiectasis. Serosal surfaces are injured by cytokine-driven inflammation (pericarditis 2/2). No fibrotic or oxidative-stress mechanism specific to DOCK11 has been described.

Molecular profiling

GTEx v8 bulk expression and HPA protein data are described in section 7. Transcriptomic or proteomic profiling of ADMIDX patient cells has not been published beyond targeted flow cytometry of FOXP3, IKZF2 and phospho-STAT5B and NFATc1 imaging. No single-cell, spatial, multi-omic or CRISPR-screen dataset exists for

this disease. One relevant screen result sits outside the disease: loss of DCAF8 causes DOCK11 accumulation, elevated CDC42 activity and loss of haematopoietic stem cell polarity, and knocking out Dock11 rescues the Dcaf8-null phenotype (PMID: 40643159, mouse). That is the reciprocal direction of the ADMIDX lesion and supports a dose-sensitive DOCK11-CDC42 axis in blood stem cells.

7. Anatomical structures affected

Organ level

Structure	UBERON	Involvement
Blood	UBERON:0000178	Primary: haemolytic anaemia, thrombocytopenia, neutropenia, leukocytosis
Bone marrow	UBERON:0002371	Primary: site of the haematopoietic lesion
Spleen	UBERON:0002106	Primary: splenomegaly (2/4), marginal zone defect
Large intestine	UBERON:0000059	Primary: Crohn disease, ulcerative colitis, diarrhoea
Small intestine	UBERON:0002108	Primary: recurrent gastroenteritis (3/4)
Skin	UBERON:0002097	Primary: panniculitis, discoid lupus
Lung	UBERON:0002048	Secondary: recurrent pneumonia, bronchiectasis
Liver	UBERON:0002107	Secondary: hepatomegaly (2/4), acute liver failure (PMID: 40107756)
Pericardium	UBERON:0002407	Secondary: pericarditis (2/2)
Kidney	UBERON:0002113	Secondary: nephrotic syndrome (1/12)
Synovial joint	UBERON:0002217	Secondary: polyarticular arthritis (2/8)
Thymus	UBERON:0002370	Abnormal thymus cell ratio in mouse
Lymph node	UBERON:0000029	Benign lymphoproliferation
Brain	UBERON:0000955	Developmental delay; seizures in one case (PMID: 41250716)

Body systems involved: haematopoietic and immune (primary), digestive, integumentary, respiratory, cardiovascular (pericardium), musculoskeletal, renal, nervous.

Tissue and cell level

Haematopoietic and lymphoid tissue is the primary target. Within the spleen, the marginal zone (UBERON:0001254) and its metallophilic macrophages show abnormal morphology in mouse knockouts. Epithelial injury in the gut is secondary to immune-mediated inflammation, with no evidence for a cell-intrinsic epithelial defect. Cell types are listed in section 6.

Subcellular level

Compartment	GO CC
Cytosol	GO:0005829
Plasma membrane	GO:0005886
Cell leading edge and filopodium	GO:0030175
Actin cytoskeleton	GO:0015629
Immunological synapse	GO:0001772
Nucleoplasm	GO:0005654

DOCK-D proteins distribute between cytosol and nucleoplasm with variable predominance across cell lines, and nuclear predominance is common for DOCK9 and DOCK11 (PMID: 34449554, in vitro). The function of nuclear DOCK11 is not established.

Localization and lateralization

Involvement is systemic and bilateral where paired organs are affected (lungs, kidneys, joints). No lateralised or asymmetric pattern is described.

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8. Temporal development

Onset. Paediatric. HPO onset annotations: juvenile 6/8, childhood 3/12, infantile 2/4, congenital 1/4. The four-patient series describes "early-onset severe immune dysregulation"; the eight-patient series describes "early-onset autoimmunity". The usual onset pattern is chronic with superimposed acute episodes. Acute liver failure as a presentation (PMID: 40107756) and infection-triggered hyperinflammation (PMID: 40274249) show that an acute catastrophic first presentation is possible.

Progression. No formal staging system exists. The course is chronic and lifelong, with an episodic autoinflammatory component (recurrent febrile episodes) layered on progressive chronic damage: bronchiectasis accumulates from repeated pneumonia, growth failure accumulates from chronic inflammation. Progression rate is variable. One 10-year-old was stable enough for watchful waiting (PMID: 41250716), while UniProt DI-06712 records death in childhood.

Remission. Spontaneous remission is not documented. Treatment-induced remission of cytopenias and colitis with corticosteroids and immunosuppression is the usual pattern, with relapse on withdrawal. Definitive remission follows allogeneic HSCT.

Critical periods. Two intervention windows follow from the mechanism. Before live BCG or other live vaccination, diagnosis prevents vaccine-strain disease. Before bronchiectasis becomes established, infection prophylaxis and immunoglobulin replacement prevent irreversible airway damage. HSCT performed before accumulated organ damage is expected to give the better outcome, which is standard for inborn errors of immunity but has not been quantified for ADMIDX.

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9. Inheritance and population

Prevalence and incidence. No prevalence or incidence estimate exists. Thirteen patients from 12 families are reported in the three index series, with isolated later cases. The disease is below the Orphanet reporting threshold. A crude upper bound from gnomAD v4 cumulative pLoF allele frequency (2.581×10^{-4}) gives a male carrier frequency of about 1.48×10^{-4}, roughly 1 in 6,780 males. ⚠ That figure is an upper bound only. The positional analysis in section 4 shows most population pLoF alleles truncate far earlier in the open reading frame than disease alleles, so the true prevalence is far lower.

Inheritance. X-linked recessive (HP:0001419). All 13 reported patients are hemizygous males. Carrier females in the reported families are described as unaffected. Skewed X-inactivation could in principle produce a manifesting carrier, but no such case is reported.

Penetrance. Appears complete in hemizygous males carrying the reported disease alleles, within the limits of ascertainment through affected probands. The gnomAD hemizygote observations do not refute complete penetrance because those alleles differ in position (Mann-Whitney $p = 0.0137$).

Expressivity. Variable, and partly predicted by allele class (section 12 and the key-findings synthesis). Within allele classes the range still spans watchful waiting to childhood death.

Genetic anticipation. Not applicable. DOCK11 is not a repeat-expansion locus.

Germline mosaicism, founder effects, consanguinity. No germline mosaicism, no founder variant and no consanguinity effect has been reported. Consanguinity is not expected to matter for an X-linked recessive condition in the way it does for autosomal recessive disease.

Carrier frequency. Obligate carrier mothers are identified by cascade testing within families. No population carrier frequency is established for pathogenic DOCK11 alleles specifically.

Population demographics. Sex ratio is effectively 100% male among reported patients. The 12 families are reported from multiple countries without ethnic or geographic clustering, and no variant shows geographic restriction. All reported patients were diagnosed in infancy, childhood or adolescence.

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10. Diagnostics

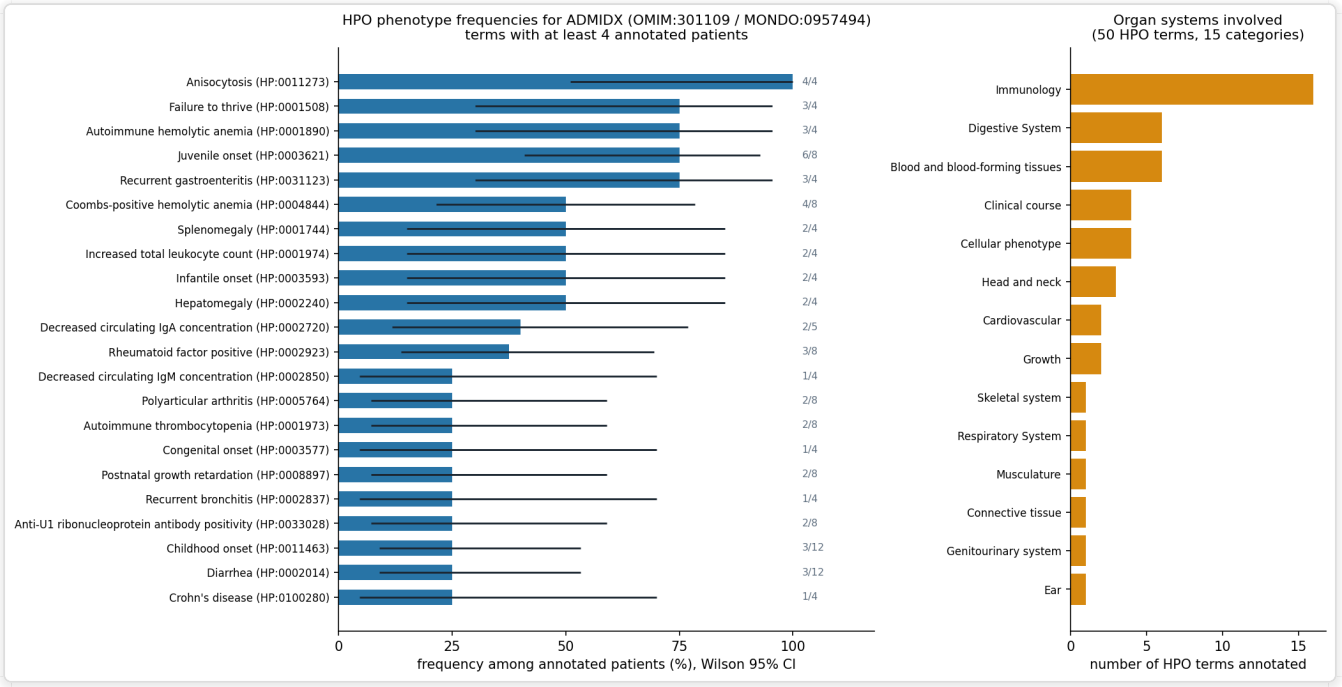


Figure 4. *HPO phenotype frequency profile for ADMIDX and the breadth of organ-system involvement. The 50 annotations span 15 HPO categories, with the largest burden in blood, immune serology, gut and growth.*

Laboratory tests

Full blood count with film review (anisocytosis, poikilocytosis, normocytic anaemia, thrombocytopenia, neutropenia), direct antiglobulin test (Coombs-positive in 4/8), reticulocyte count, haptoglobin, LDH and bilirubin for haemolysis, CRP, ESR and ferritin for inflammation, serum immunoglobulins including IgA

(decreased 2/5), vaccine-response serology, autoantibody panel including antinuclear antibody, anti-U1 RNP (2/8) and rheumatoid factor (3/8), proinflammatory cytokine panel (elevated in the ADMIDX case report, PMID: 41250716), liver function tests, urinalysis and urine protein quantification for nephrotic syndrome.

Functional and mechanism-specific assays

Because most DOCK11 missense variants return as VUS, functional testing is part of the diagnostic path rather than an optional extra:

- DOCK11 protein level by immunoblot in patient peripheral blood mononuclear cells, which distinguishes expression-null from hypomorphic missense and therefore carries prognostic meaning.
- CDC42-GTP loading assay (GST-PAK pulldown) in patient cells ("impaired CDC42 activation in all four patients", PMID: 37342957).
- Filopodium formation assay by fluorescence microscopy.
- Treg immunophenotyping for FOXP3 and IKZF2 (PMID: 36952639) and phospho-STAT5B after IL-2 stimulation.
- NFATc1 nuclear translocation imaging in stimulated T cells (PMID: 37342957).

A published neonatal case shows negative functional studies resolving a DOCK11 VUS and guiding care (PMID: 42382659).

Imaging, electrophysiology, biopsy and pathology

Chest CT for bronchiectasis. Abdominal ultrasound or MRI for hepatosplenomegaly. Echocardiography for pericardial effusion. Endoscopy with intestinal biopsy for IBD-like colitis. Skin biopsy for panniculitis. Bone marrow examination to exclude other causes of cytopenia. Renal biopsy if nephrotic syndrome is present. EEG if seizures occur (PMID: 41250716). ✖ No ADMIDX-specific imaging or histopathological signature has been defined, and no cardiac, pulmonary-function or nerve-conduction abnormality is specific to this disease.

Genetic testing

The reported route to diagnosis has been whole exome sequencing, whole genome sequencing or a targeted inborn-errors-of-immunity gene panel. DOCK11 is now included in modern primary immunodeficiency and autoinflammatory panels; the ADMIDX case report was diagnosed by panel (PMID: 41250716). WES or a panel is the first-line test. WGS adds detection of deep intronic and structural variants. Single-gene DOCK11 testing is appropriate only for cascade testing of a known familial variant.

✗ Chromosomal microarray, karyotyping, FISH, mitochondrial DNA testing and repeat expansion testing have no role in diagnosing ADMIDX. Microarray would only detect the large Xq copy-number events that are classified for other contiguous-gene syndromes.

Variant interpretation uses ACMG/AMP criteria on NM_144658.4. Truncating and canonical splice alleles at codons 1252-2012 are supported by PVS1 plus segregation. Missense alleles will usually need PS3 from the functional assays above to move off VUS.

Omics-based diagnostics

✗ RNA sequencing, proteomics, metabolomics, epigenomics and liquid biopsy have no established diagnostic role in ADMIDX. RNA sequencing of patient blood could confirm the effect of the splice alleles (c.392+1G>A, c.4582-1G>A) on transcript structure, which is a reasonable adjunct but is not standard practice.

Clinical criteria and when to suspect

No formal diagnostic criteria exist. The clinical trigger from the actinopathy review is:

> "Diagnosis should be considered primarily when encountering an early-onset autoinflammatory skin and digestive disorder, along with a primary immunodeficiency and either thrombocytopenia or a bleeding tendency" (PMID: 39644982)

Its description of the shared signature applies to ADMIDX: "These diseases typically manifest in the neonatal period and variably combine a primary immunodeficiency of varying severity, cytopenia (particularly thrombocytopenia), autoinflammatory manifestations primarily affecting the skin and digestive system, as well as atopic and autoimmune features".

Differential diagnosis

Condition	Gene	Distinguishing features
Wiskott-Aldrich syndrome	WAS (X-linked)	Microthrombocytopenia with small platelets, eczema; anaemia with anisopoikilocytosis is not typical
DOCK8 deficiency	DOCK8 (AR)	Severe atopy, cutaneous viral infection, very high IgE
DOCK2 deficiency	DOCK2 (AR)	Early severe combined immunodeficiency, invasive viral infection
ARPC1B deficiency	ARPC1B (AR)	Platelet abnormality, vasculitis, eosinophilia
CDC42 disease (Takenouchi-Kosaki)	CDC42 (AD)	Developmental syndrome with dysmorphism; same pathway, different genetics
ALPS	FAS, FASLG, CASP10	Double-negative T cell expansion, lymphoproliferation without anisopoikilocytosis
CTLA4 haploinsufficiency, LRBA deficiency	CTLA4, LRBA	Autoimmune cytopenia plus IBD plus lymphoproliferation; found alongside DOCK11 in testing of paediatric AIC with IBD (PMID: 39155467)
Monogenic very-early-onset IBD	IL10RA, XIAP	Colitis dominates without the autoantibody profile
Sporadic Evans syndrome	none	No X-linked family history, no autoinflammation

Screening

ADMIDX is not included in any newborn screening programme and has no screening biomarker. The SCID TREC assay would not detect it. Cascade genetic testing of at-risk maternal relatives after a proband is identified is the only screening that applies.

11. Outcome and prognosis

⚠ No survival analysis, life expectancy estimate, mortality rate or quality-of-life measurement exists for ADMIDX. With 13 published patients and no registry, this section is necessarily qualitative.

Mortality. UniProt disease entry DI-06712 records that death in childhood has been reported. No case fatality rate can be computed. Acute liver failure as a presenting feature (PMID: 40107756) identifies one route to early death.

Morbidity. The documented burden is chronic transfusion-requiring or immunosuppression-requiring haemolytic anaemia, chronic colitis, recurrent hospitalisation for febrile autoinflammatory episodes, progressive bronchiectasis in patients with expression-null alleles, failure to thrive (3/4), postnatal growth retardation (2/8) and developmental delay. Disability outcomes have not been measured against ICF or any other framework.

Complications. Bronchiectasis from recurrent pneumonia, disseminated BCG after live vaccination, nephrotic syndrome (1/12), acute liver failure, and the standard complications of long-term corticosteroid and immunosuppressive therapy.

Recovery potential. Untreated, the disease is chronic and progressive. Immunosuppression controls but does not cure. Allogeneic HSCT is expected to be curative because disease is confined to the haematopoietic compartment, although outcome data in DOCK11 deficiency specifically are not published.

Prognostic factors. The strongest candidate prognostic marker found here is allele class and residual DOCK11 protein. Expression-null alleles track with autoinflammation and recurrent pneumonia, which carries the bronchiectasis risk; missense alleles track with autoantibody disease, which carries the cytopenia and lupus risk (Fisher $p = 0.035$, $n = 13$, zero cell). ⚠ This is group-level data from a published re-evaluation rather than per-patient chart review and should be treated as a hypothesis for prospective testing. No prognostic biomarker has been validated.

12. Treatment

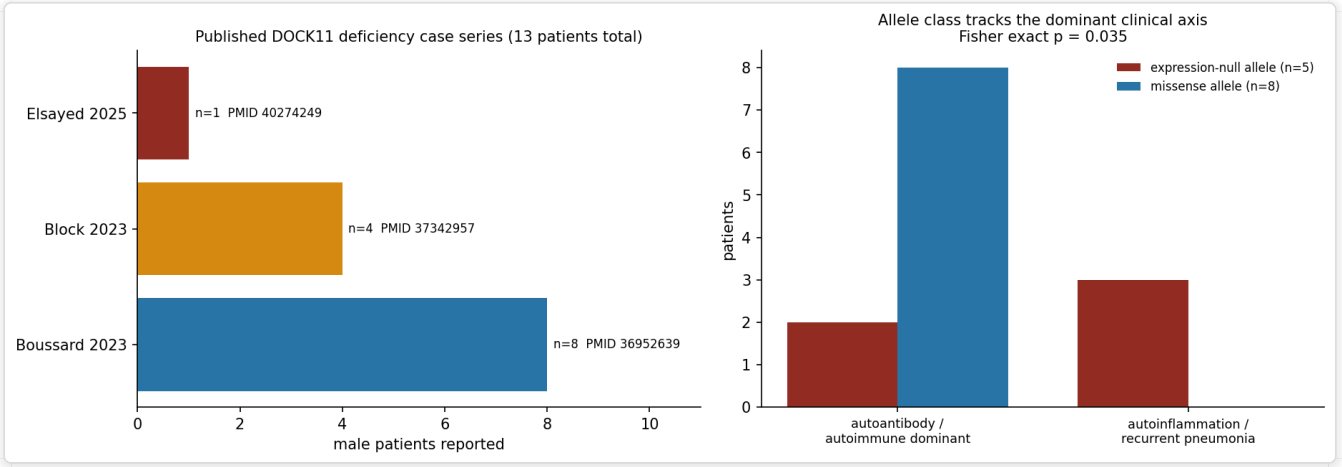


Figure 5. *Synthesis of the 13 published DOCK11 deficiency patients from 12 families, and the association between allele class and the dominant phenotype axis. Expression-null alleles (n = 5) track with autoinflammation and recurrent pneumonia; missense alleles (n = 8) track with autoantibody-driven autoimmunity (Fisher exact p = 0.035, with a zero cell so the odds ratio is uninformative).*

Definitive treatment

> "In most cases, the severity of the conditions necessitates allogeneic marrow transplantation as a treatm[ent]" (PMID: 39644982, review of monogenic autoinflammatory actinopathies covering DOCK11 alongside DOCK2, DOCK8, WAS, ARPC1B and CDC42 disease)

✅ The mechanistic rationale is specific to this disease. DOCK11 is expressed in every human tissue (GTEx: 45.4 TPM subcutaneous adipose, 31.9 tibial artery, 21.2 spleen; HPA "Low tissue specificity, Detected in all"), yet disease is confined to the haematopoietic compartment. Replacing that compartment should therefore correct the phenotype in full, which predicts cure rather than control. No HSCT outcome series in DOCK11 deficiency has been published, so this is a mechanistic prediction supported by the general practice in actinopathies.

Treatment table with NCIT terms

Treatment	Class and mechanism	NCIT	Indication in ADMIDX
Allogeneic haematopoietic stem cell transplantation	Cell therapy, replaces the DOCK11-deficient haematopoietic compartment	NCIT:C15431 (allogeneic bone marrow transplantation)	Severe disease; the only curative option
Prednisolone, methylprednisolone	Corticosteroid, broad anti-inflammatory	NCIT:C769 (prednisolone), NCIT:C629 (methylprednisolone)	Autoimmune cytopenia, colitis, serositis, flares
Intravenous immunoglobulin	Immunoglobulin replacement and immunomodulation	NCIT:C579	Low IgA and antibody deficiency; also for immune cytopenia
Rituximab	Anti-CD20 monoclonal antibody, B cell depletion	NCIT:C1702	Refractory autoimmune haemolytic anaemia and thrombocytopenia
Ciclosporin, tacrolimus	Calcineurin inhibitor, blocks NFAT activation	NCIT:C405 (ciclosporin), NCIT:C1262 (tacrolimus)	Rational for the NFATc1 hyperactivation axis; not formally tested in DOCK11
Ruxolitinib, baricitinib, tofacitinib	JAK1/2 or JAK1/3 inhibitor	NCIT:C82364 (ruxolitinib), NCIT:C98234 (baricitinib), NCIT:C71146 (tofacitinib)	Autoinflammation and interferon-driven features; not formally tested in DOCK11
Mycophenolate mofetil, azathioprine, sirolimus	Antiproliferative or mTOR inhibitor immunosuppression	NCIT:C1799 (mycophenolate mofetil), NCIT:C296 (azathioprine), NCIT:C1212 (sirolimus)	Steroid-sparing maintenance for cytopenia and autoimmunity
Infliximab, adalimumab	TNF blockade	NCIT:C1703 (infliximab), NCIT:C1490 (adalimumab)	IBD-like colitis
Anakinra	IL-1 receptor antagonist	NCIT:C1593	Autoinflammatory fever and serositis, by analogy with other autoinflammatory disease
	Antimicrobial		

Treatment	Class and mechanism	NCIT	Indication in ADMIDX
Co-trimoxazole prophylaxis		NCIT:C250 (antibiotic therapy)	Recurrent pneumonia, bronchiectasis
Red cell transfusion	Supportive	NCIT:C15360 (blood transfusion)	Severe haemolytic anaemia
Nutritional support	Supportive	NCIT:C15339 (nutritional support)	Failure to thrive
Airway clearance physiotherapy	Rehabilitative	NCIT:C15417 (physical therapy)	Bronchiectasis
Watchful waiting	Observation	NCIT:C96109 (watchful waiting)	Documented in a clinically stable 10-year-old (PMID: 41250716)

⚠ Calcineurin inhibition and JAK inhibition are inferences from the demonstrated NFATc1 hyperactivation and impaired STAT5B signalling in patient cells. Neither has been tested in a DOCK11 cohort. The review states the therapeutic gap directly:

> "The complete pathophysiology of these diseases is not yet fully understood, and further studies are required to elucidate the underlying mechanisms, which could guide therapeutic choices" (PMID: 39644982)

Advanced therapeutics

✖ No gene therapy, gene editing, RNA-based therapy or targeted small molecule exists for ADMIDX. A 2073-amino-acid coding sequence (6.2 kb) exceeds the packaging capacity of AAV, which makes lentiviral gene-corrected autologous HSC therapy the more plausible future route than AAV gene replacement. That direction is untested. Nucleic-acid drugs targeting DOCK11 have been developed, but to **suppress** DOCK11 for hepatitis B (PMID: 39109217, PMID: 35660020), the opposite of what ADMIDX needs, and a caution for any future DOCK11-directed antiviral in patients with partial DOCK11 function.

Pharmacogenomics, surgery, trials

No DOCK11 pharmacogenomic interaction is established. TPMT and NUDT15 genotyping before azathioprine follows standard CPIC practice and is not DOCK11-specific. Surgery is limited to complications: bowel resection for refractory IBD, splenectomy for refractory cytopenia (used cautiously given the infection risk in this disease), central venous access for transfusion. ✕ No interventional clinical trial is registered for ADMIDX or DOCK11 deficiency, so no NCT identifier applies.

Treatment strategy

A reasonable algorithm, built from the mechanism and the reported practice rather than from a guideline: confirm the genetic diagnosis and measure residual DOCK11 protein and CDC42-GTP loading; stop live vaccines immediately; start immunoglobulin replacement and antibiotic prophylaxis if antibody deficiency or recurrent pneumonia is present; control cytopenia and colitis with corticosteroids plus a steroid-sparing agent; escalate to rituximab for refractory cytopenia or anti-TNF for refractory colitis; assess for allogeneic HSCT early in patients with expression-null alleles, bronchiectasis risk, or disease refractory to immunosuppression. Genotype-guided care here means using allele class to anticipate which axis will dominate.

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13. Prevention

Primary prevention. ✕ Disease occurrence in a hemizygous male cannot be prevented once the variant is inherited. The only primary prevention is reproductive: genetic counselling of carrier families, with preimplantation genetic testing for monogenic disease (PGT-M) or prenatal diagnosis by chorionic villus sampling or amniocentesis where the familial variant is known. A carrier mother has a 50% risk per male pregnancy. All daughters of an affected male are obligate carriers and no son of an affected male inherits the variant.

Secondary prevention. Cascade genetic testing of at-risk maternal male relatives allows diagnosis before a severe first presentation. There is no population newborn screen for DOCK11 and no biochemical marker that would support one.

Tertiary prevention. This is where most preventable harm sits. Avoidance of live attenuated vaccines, BCG above all, prevents vaccine-strain disease (BCGitis 1/4). Antibiotic prophylaxis and immunoglobulin replacement prevent the recurrent pneumonia that leads to irreversible bronchiectasis. Infection surveillance during immunosuppression, nutritional support for failure to thrive, surveillance for autoimmune cytopenia and for nephrotic syndrome, and timely HSCT before accumulated organ damage all apply.

Immunization. Inactivated vaccines (influenza, conjugate pneumococcal, inactivated poliovirus) are indicated and should be given, with the caveat that antibody responses may be poor in patients with low IgA. Live vaccines (BCG, measles-mumps-rubella, varicella, oral poliovirus, rotavirus, live attenuated influenza) are contraindicated once the diagnosis is known.

Behavioural interventions and public health measures. ✕ Not applicable. No lifestyle modification alters ADMIDX risk or course beyond standard infection-avoidance precautions for an immunocompromised child. No environmental or public-health intervention applies to a monogenic X-linked disease.

14. Other species and natural disease

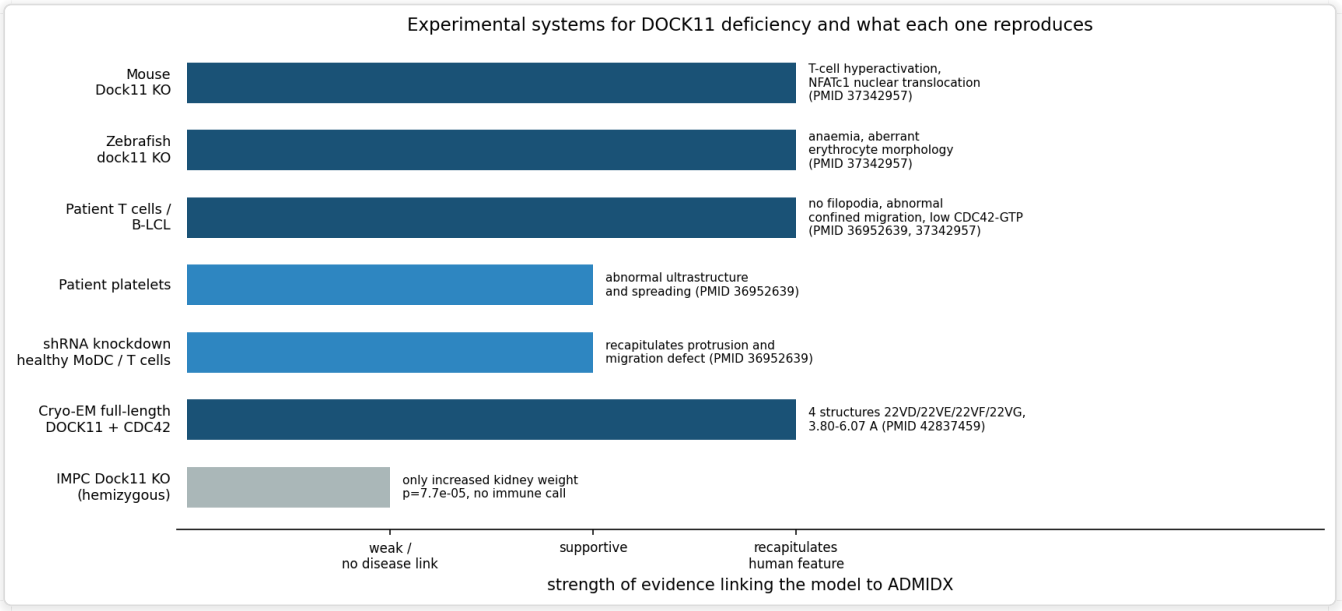


Figure 6. *Mouse Dock11 phenotype statements curated in MGI, with a summary of which model system supplies evidence for which arm of the human ADMIDX phenotype.*

Orthologs

Species	NCBI Taxon	Gene	Database ID	Prediction methods
Mus musculus	NCBITaxon:10090	Dock11	MGI:1923224, NCBI Gene 75974	10, high confidence
Rattus norvegicus	NCBITaxon:10116	Dock11	RGD:1564707, NCBI Gene 313438	10, high confidence
Danio rerio	NCBITaxon:7955	dock11	ZDB-GENE-060503-196, NCBI Gene 799686	moderate confidence
Xenopus tropicalis	NCBITaxon:8364	dock11	XB-GENE-921713	9
Xenopus laevis	NCBITaxon:8355	dock11.L	not assigned	not assigned
Drosophila melanogaster	NCBITaxon:7227	Ziz	FBgn0260486	9
Caenorhabditis elegans	NCBITaxon:6239	dock-11	WBGene00009065	8

Natural disease in other species

No naturally occurring DOCK11 disease is catalogued in OMIA for any species. No breed-associated DOCK11 disorder exists, so no VBO identifier applies. There is no veterinary relevance and no zoonotic or cross-species transmission dimension; ADMIDX is a germline monogenic disease and is not transmissible.

Two observational genetic associations involving DOCK11 in non-human species exist but describe traits rather than disease models. In the critically endangered King Island scrubtit (*Acanthornis magna greeniana*), a locus within DOCK11 was among six significantly associated with crown baldness observed in 8/15 King Island birds and 0/55 Tasmanian birds, which the authors link to early feather development (PMID: 38814752). In chickens, DOCK11 was identified as a candidate gene regulating HDL cholesterol in a GWAS of 206 males (PMID: 37792060). Neither is an ADMIDX phenocopy.

Comparative biology and conservation

The core molecular job of DOCK11, CDC42-dependent filopodial actin assembly, predates the vertebrate immune system. In C. elegans, "cdc-42 and the guanine nucleotide exchange factor dock-11 are also required for branch formation" in PLM neuron collateral branching, acting with the Arp2/3 activator toca-1 (PMID: 41278672, model organism). The immune functions are a vertebrate elaboration on that conserved module.

One comparative difference matters for interpretation. Mouse Zizimin2 protein expression "is also restricted to lymphoid tissues and lymphocytes" (PMID: 22494997), and the original cloning paper described expression predominantly in lymphocytes (PMID: 15710388). Human data do not reproduce that restriction, so the mouse expression pattern should not be transferred to human reasoning about which tissues are at risk.

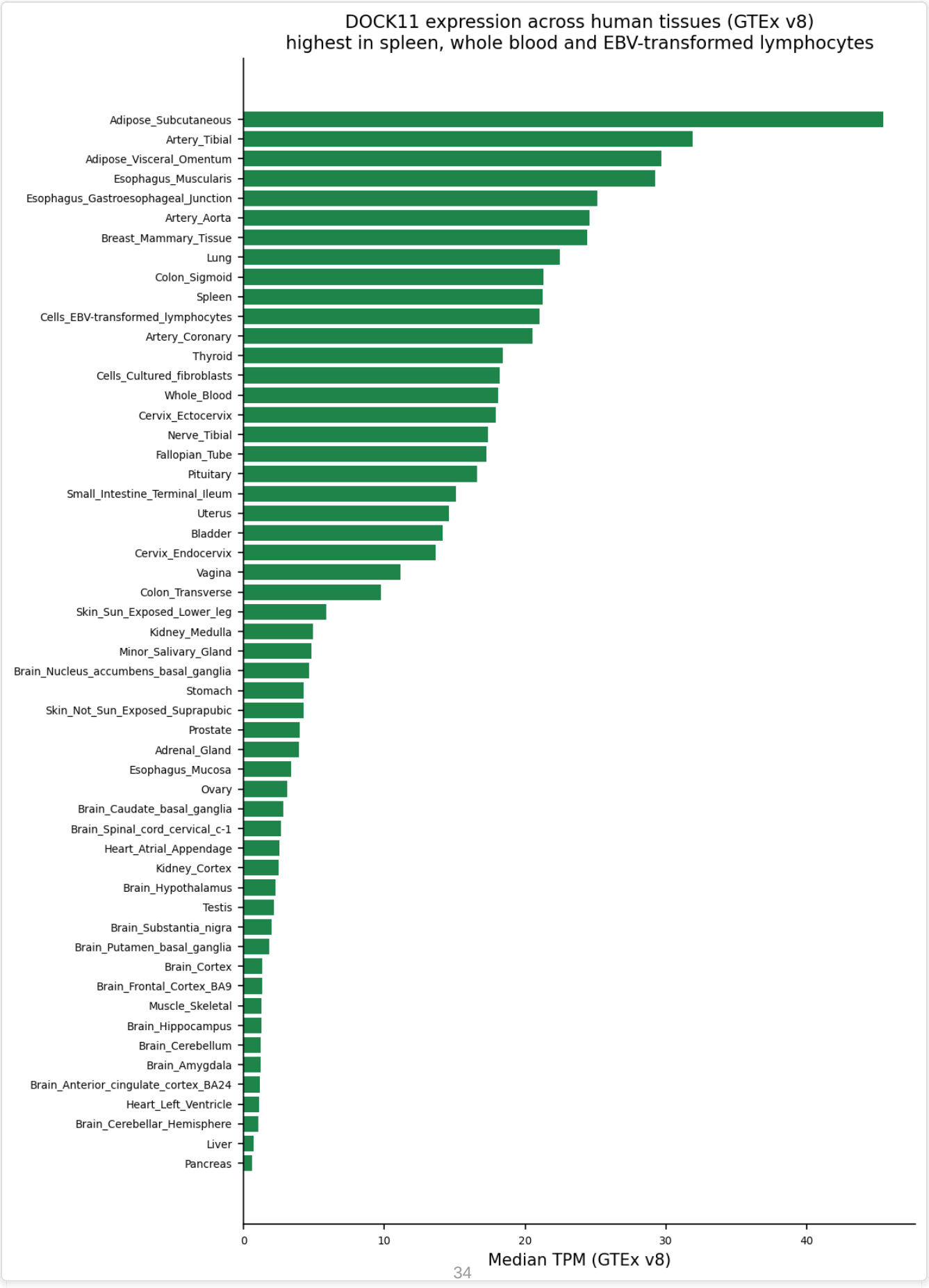

DOCK11 expression across human tissues (GTEx v8)
highest in spleen, whole blood and EBV-transformed lymphocytes
Adipose_Subcutaneous
Artery_Tibial
Adipose_Visceral_Omentum
Esophagus_Muscularis
Esophagus_Gastroesophageal_Junction
Artery_Aorta
Breast_Mammary_Tissue
Lung
Colon_Sigmoid
Spleen
Cells_EBV-transformed_lymphocytes
Artery_Coronary
Thyroid
Cells_Cultured_fibroblasts
Whole_Blood
Cervix_Ectocervix
Nerve_Tibial
Fallopian_Tube
Pituitary
Small_Intestine_Terminal_Ileum
Uterus
Bladder
Cervix_Endocervix
Vagina
Colon_Transverse
Skin_Sun_Exposed_Lower_leg
Kidney_Medulla
Minor_Salivary_Gland
Brain_Nucleus_accumbens_basal_ganglia
Stomach
Skin_Not_Sun_Exposed_Suprapubic
Prostate
Adrenal_Gland
Esophagus_Mucosa
Ovary
Brain_Caudate_basal_ganglia
Brain_Spinal_cord_cervical_c-1
Heart_Atrial_Appendage
Kidney_Cortex
Brain_Hypothalamus
Testis
Brain_Substantia_nigra
Brain_Putamen_basal_ganglia
Brain_Cortex
Brain_Frontal_Cortex_BA9
Muscle_Skeletal
Brain_Hippocampus
Brain_Cerebellum
Brain_Amygdala
Brain_Anterior_cingulate_cortex_BA24
Heart_Left_Ventricle
Brain_Cerebellar_Hemisphere
Liver
Pancreas
0
10
20
30
40
Median TPM (GTEx v8)

Figure 7. *DOCK11 median expression across GTEx v8 tissues. Subcutaneous adipose (45.4 TPM) and tibial artery (31.9 TPM) exceed spleen (21.2 TPM) and EBV-transformed lymphocytes (21.0 TPM), which refutes the hypothesis that immune-restricted disease reflects immune-restricted expression.*

15. Model organisms

Mouse

Six Dock11 alleles are catalogued in MGI: **Dock11-tm1Mmar** and **Dock11-tm1.1Mmar** (Maruyama lab, conventional and B-cell-conditional knockout), **Dock11-tm1Thar**, and the KOMP series **tm1e(KOMP)Wtsi**, **tm2a(KOMP)Wtsi**, **tm2b(KOMP)Wtsi**. Curated phenotypes: decreased marginal zone B cell number, abnormal spleen marginal zone morphology, abnormal metallophilic macrophage morphology, abnormal thymus cell ratio (all Dock11-tm1.1Mmar, PMID: 25729399), impaired macrophage chemotaxis (Dock11-tm1Thar), plus IMPC calls on Dock11-tm2b(KOMP)Wtsi hemizygotes for increased kidney weight and abnormal eye morphology.

> "Ziz2 KO mice had a higher percentage of early bone marrow B cells (Fraction A), but a reduced fraction of marginal zone (MZ) B cells" (PMID: 25729399, model organism)
>
> "as well as the T cells from Dock11-knockout mice, showed overt activation and production of proinflammatory cytokines that were associated with an increased degree of nuclear translocation of nuclear factor of activated T cell 1 (NFATc1)" (PMID: 37342957, model organism)

Mouse models also cover secondary humoral immunity: the lack of DOCK11 in B cells impaired induction of antibody-producing cells on secondary immunisation with protein antigen, and that defect was B-cell-extrinsic, recovered by adoptive transfer of cognate T cells (PMID: 34980182). Mouse Zizimin2 induces filopodia in bone marrow-derived dendritic cells (PMID: 22494997).

⊗ **A negative result worth recording.** The IMPC primary phenotyping screen on hemizygous Dock11 knockouts returned one significant and immunologically irrelevant call, increased kidney weight ($p = 7.7 \times 10^{-5}$, effect size 0.044), with no immune hit. Standard unchallenged phenotyping pipelines miss this gene. The immune phenotypes require either targeted immunophenotyping or an infectious or inflammatory challenge.

Zebrafish

A dock11-knockout zebrafish was generated for the human study and is the only model that reproduces the erythrocyte phenotype:

> "Anemia and aberrant erythrocyte morphologic features were recapitulated in a newly generated dock11-knockout zebrafish model" (PMID: 37342957, model organism)

dock11 knockdown in zebrafish also disrupts embryogenesis (PMID: 41503681).

Invertebrate and cellular systems

C. elegans dock-11 is required with cdc-42 and toca-1 for PLM neuron collateral branching (PMID: 41278672), which gives a tractable genetic system for the core actin module. Cell-line work on DOCK-D subcellular distribution used 11 cell lines and produced a validated DOCK10 antiserum (PMID: 34449554). Patient-derived peripheral blood mononuclear cells are the primary human in vitro system, used for CDC42-GTP pulldown, filopodium imaging, Treg phenotyping and NFATc1 translocation. ✗ No ADMIDX iPSC line or organoid model has been reported.

Phenotype recapitulation summary

Human feature	Mouse	Zebrafish	C. elegans	Patient cells
Impaired CDC42 activation	✓	?	✓ genetic	✓
T cell hyperactivation, NFATc1	✓	not tested	not applicable	✓
Treg FOXP3 and IKZF2 loss	?	not tested	not applicable	✓
Marginal zone B cell loss	✓	not tested	not applicable	?
Impaired macrophage chemotaxis	✓	not tested	not applicable	?
Anaemia with anisopoikilocytosis	✗	✓	not applicable	not applicable
Autoantibody autoimmunity, SLE	✗	not tested	not applicable	✓
IBD-like colitis	✗	not tested	not applicable	not applicable

⚠ No single animal reproduces ADMIDX. Model choice should follow the question: mouse for lymphocyte and macrophage biology, zebrafish for erythropoiesis, patient cells for migration and CDC42-GTP readouts. The autoantibody autoimmunity and the colitis have no animal model at all, which is the largest gap in the model inventory.

Resources. MGI (mouse), IMPC and KOMP (knockout alleles), IMSR, EMMA and MMRRC (strain distribution), ZFIN (zebrafish), WormBase (C. elegans), FlyBase (Drosophila Ziz), Alliance of Genome Resources (integrated orthology and phenotype).

Mechanistic model and interpretation

The disease has one upstream lesion and five downstream branches. Upstream: DOCK11 fails to load GTP onto CDC42 at the plasma membrane of haematopoietic cells. Everything else follows from the cell type in which that failure occurs.

The structural work converts this from a dose-response story into a threshold story. DOCK11 binds nucleotide-free CDC42 at the DOCKER catalytic domain and CDC42-GTP at a distal armadillo-repeat site; the second binding event drives membrane recruitment and raises exchange activity. That is a positive feedback loop, and a feedback loop has an ignition threshold. 💡 This resolves what otherwise looks like a contradiction in the clinical data: missense alleles that only reduce DOCK11 protein produce disease as severe as alleles that abolish it. A loop that does not ignite gives zero output regardless of how much substrate is present.

The same structure explains the gnomAD positional result. Disease alleles truncate at codons 1252 to 2012, which removes or disables the DOCKER domain while leaving the PH (165-272) and C2/DHR-1 (640-818) membrane-contact modules intact. A protein like that still reaches the membrane and still occupies the site, but cannot catalyse exchange: a dead-end CDC42 scaffold. Population pLoF alleles truncate at median codon 921, before those features are assembled into a functional membrane-targeted unit, and those alleles are compatible with hemizygous life. ⚠ The dead-end-scaffold model is inferred from variant position mapped onto the structures and has not been tested directly.

Observation	Interpretation	Evidence type
59 hemizygous pLoF carriers in gnomAD v4	Not a penetrance problem. Those alleles truncate at median codon 921 against 1464 for disease alleles (p = 0.0137)	Computational
Missense alleles as severe as nulls	Thresholded positive feedback, not a linear dose-response	Structural plus clinical
Null alleles give autoinflammation plus pneumonia; missense gives autoantibodies	Dose effect on one pathway: complete loss removes myeloid and erythroid function too, partial loss hits Treg identity first	Clinical, n = 13, Fisher p = 0.035
DOCK11 expressed in all tissues, disease only in blood	GEF redundancy (DOCK9, DOCK10, intersectin, FGD1, VAV) covers non-haematopoietic tissue	Inferred from expression plus phenotype
HSCT cures	Follows from the row above: the diseased compartment is replaceable	Inferred plus clinical practice
IMPC primary screen finds nothing immune	Unchallenged phenotyping misses actin regulators of immunity	Model organism, negative

The DCAF8 result gives the reciprocal test of the dose model. Loss of DCAF8 causes DOCK11 accumulation, elevated CDC42 activity and loss of haematopoietic stem cell polarity, and deleting Dock11 rescues it (PMID: 40643159). Too much DOCK11-CDC42 activity damages blood stem cells; too little causes ADMIDX. The axis is dose-sensitive in both directions in the haematopoietic compartment specifically, which is consistent with the redundancy argument for why other tissues are spared.

Key findings with statistical evidence

F1. ADMIDX is caused by hemizygous loss-of-function variants in DOCK11, a constrained X-linked CDC42 GEF. gnomAD v4 constraint: observed/expected LoF = 0.414 (LOEUF 0.505, lof_z 6.46), observed/expected missense = 0.758 (mis_z 4.05), syn_z 0.32. Two index cohorts reported 12 male patients, 8 from 7 unrelated families with hemizygous missense variants reducing DOCK11 expression and 4 from 4 unrelated families with LoF variants abolishing protein or impairing CDC42 activation. Low pLI (0.103) is expected for an X-linked gene and does not argue against pathogenicity.

F2. The phenotype is quantified by 50 HPO annotations spanning 15 organ-system categories. Anisocytosis (HP:0011273) at 4/4 with Wilson 95% CI 51-100% is the most frequent single annotation, followed by autoimmune haemolytic anaemia 3/4, recurrent gastroenteritis 3/4, failure to thrive 3/4 and juvenile onset 6/8. Coombs-positive haemolytic anaemia is 4/8. The anaemia is the most penetrant single feature, which is unusual among actinopathies and points to a role for DOCK11 in erythropoiesis.

F3. Allele class splits the clinical axis. Scoring 5 expression-null against 8 missense patients on the published dominant-axis assignment gives Fisher exact p = 0.035 with a zero cell, so the odds ratio is uninformative. Shared features across both groups: early-onset immune dysregulation, autoimmune cytopenia, inflammatory bowel disease, benign lymphoproliferation, skin involvement.

F4. Cryo-EM defines a membrane-dependent positive feedback loop. Four structures at 3.80-6.07 Å resolution show a U-shaped dimer with two CDC42 sites. All seven ClinVar DOCK11-specific P/LP alleles truncate at or before the end of the DOCKER domain (codon 2036).

F5. Broad expression refutes the tissue-restriction hypothesis. GTEx v8 median TPM: subcutaneous adipose 45.4, tibial artery 31.9, visceral adipose 29.7, oesophagus muscularis 29.2, gastro-oesophageal junction 25.1, aorta 24.6, breast 24.4, lung 22.5, sigmoid colon 21.3, spleen 21.2, EBV-transformed lymphocytes 21.0. HPA: "Low tissue specificity", "Detected in all", "Low immune cell specificity".

F6. Population pLoF carriers truncate earlier than disease alleles. 365 LOFTEE high-confidence pLoF variants, 139 PASS, 281 pLoF alleles, 59 hemizygous male observations, cumulative pLoF AF 2.581×10^{-4}. Of the 23 hemizygote-observed alleles with a parseable position, median codon 921 against 1464 for five disease alleles: Mann-Whitney U = 21, p = 0.0137, rank-biserial −0.635, with 3/23 (13%) at or after codon 1609.

F7. ClinVar interpretation is immature. 600 records: 14 Pathogenic, 6 Likely pathogenic, 173 VUS, 14 Likely benign, 1 Benign, 3 Conflicting, 389 unclassified. Only 7 of the 20 P/LP are DOCK11-specific small variants; the other 13 are large Xq copy-number events classified for Klinefelter syndrome or Menkes disease.

F8. No single model organism reproduces the disease. Mouse covers marginal zone B cells, macrophage chemotaxis and T cell hyperactivation; zebrafish covers the anaemia; the IMPC primary screen returned only increased kidney weight ($p = 7.7 \times 10^{-5}$).

Evidence base

PMID	Study type	What it establishes	Relation to findings
36952639	Human clinical plus in vitro	8 males, 7 families, hemizygous missense with reduced DOCK11; Treg FOXP3 and IKZF2 loss	Supports the missense-hypomorph arm and the Treg mechanism
37342957	Human clinical, mouse, zebrafish	4 males, 4 families; impaired CDC42 activation; NFATc1 hyperactivation; zebrafish anaemia	Supports the null arm, the CDC42 step and the erythroid branch
40274249	Human clinical plus review	c.3754C>T p.(Gln1252Ter) with absent protein; allele-class to phenotype-axis split	Sole source of the genotype-phenotype dichotomy
42837459	Structural, biochemical, cellular	Four cryo-EM structures; membrane-dependent CDC42 positive feedback; broad expression	Supplies the threshold model and independently confirms the expression finding
39644982	Review	Actinopathy clinical signature; HSCT necessity; absence of targeted therapy	Supports the treatment and diagnostic-trigger sections
15710388	In vitro	Zizimin2 binds and activates CDC42, not TC10 or TCL	Establishes GTPase specificity
22494997	Model organism	Mouse Zizimin2 induces filopodia in dendritic cells; lymphoid-restricted protein	Supports the filopodium step; its expression claim conflicts with human GTEx
25729399	Model organism	Marginal zone B cell reduction in Ziz2 KO mice	Supports branch C
34980182	Model organism	Impaired secondary humoral response, B-cell-extrinsic	Supports branch C and refines it as T-cell-help dependent
41278672	Model organism	cdc-42 and dock-11 required for C. elegans neurite branching	Shows the actin module predates vertebrate immunity
40107756	Human clinical	DOCK11 deficiency presenting as acute liver failure	Extends the organ range beyond blood

PMID	Study type	What it establishes	Relation to findings
41250716	Human clinical	10-year-old with fever, seizures, splenomegaly, elevated cytokines; panel diagnosis; watchful waiting	Shows the mild end of the severity range and the diagnostic route
40643159	Model organism	DCAF8 loss gives DOCK11 accumulation, CDC42 overactivity, HSC polarity loss, rescued by Dock11 KO	Reciprocal evidence for a dose-sensitive DOCK11-CDC42 axis in blood
39155467	Human clinical cohort	DOCK11 variant in 1 of 10 genetically tested children with autoimmune cytopenia plus IBD	Places DOCK11 in that differential
42382659	Human clinical	Negative functional studies resolve a neonatal DOCK11 VUS	Supports functional testing in the diagnostic path
40811145	Human clinical	Disseminated BCG in an infant with multiple gene defects including DOCK11 exon 13	Weak support for the BCG caution; DOCK11 is not the sole cause in that case
34449554	In vitro	DOCK-D proteins show nuclear predominance in several cell lines	Raises an unresolved question about nuclear DOCK11
38814752	Comparative genomics	DOCK11 locus associated with crown baldness in King Island scrubtit	A trait association, not a disease model
37792060	Comparative genomics	DOCK11 a candidate gene for HDL cholesterol in chickens	A trait association, not a disease model
36270602, 38793626, 37243264, 42300748, 35660020, 39109217, 40725188	In vitro and mouse	DOCK11 as a hepatitis B host factor for cccDNA formation and maintenance	Separate biology; relevant as a caution for DOCK11-suppressing drugs

Verbatim quotes supporting the main claims

1. "We identified rare, X-linked germline mutations in DOCK11 in the patients, leading to a loss of protein expression in two patients and impaired CDC42 activation in all four patients." (PMID: 37342957, human clinical plus in vitro)

2. "We studied 8 male patients, from 7 unrelated families, with hemizygous DOCK11 missense variants leading to reduced DOCK11 expression." (PMID: 36952639, human clinical)
3. "four patients from four unrelated families who presented with infections, early-onset severe immune dysregulation, normocytic anemia of variable severity associated with anisopoikilocytosis, and developmental delay" (PMID: 37342957, human clinical)
4. "The patients were presenting with early-onset autoimmunity, including cytopenia, systemic lupus erythematosus, skin, and digestive manifestations." (PMID: 36952639, human clinical)
5. "variants leading to the complete loss of DOCK11 expression and consequently function rather associate with autoinflammation and recurrent pneumonias, while missense variants, primarily associate with autoantibody-related autoimmune features" (PMID: 40274249, human clinical review)
6. "we also observed abnormal regulatory T-cell (Treg) phenotype with profoundly reduced FOXP3 and IKZF2 expression" (PMID: 36952639, human clinical)
7. "showed overt activation and production of proinflammatory cytokines that were associated with an increased degree of nuclear translocation of nuclear factor of activated T cell 1 (NFATc1)" (PMID: 37342957, human clinical plus model organism)
8. "DOCK11 predominantly adopts a U-shaped dimer that binds to nucleotide-free Cdc42 via the catalytic domain, whereas activated Cdc42 engages a distal site within the armadillo-repeat domain." (PMID: 42837459, structural)
9. "binding of activated Cdc42 is critical for enhancing the membrane-dependent nucleotide exchange activity of DOCK11, promoting its localization to the plasma membrane, and facilitating intracellular activation of Cdc42" (PMID: 42837459, structural plus biochemical)
10. "The guanine nucleotide exchange factor DOCK11 is widely expressed across tissues and activates Cdc42, a Rho family GTPase that regulates cytoskeletal remodeling and cell polarity" (PMID: 42837459, computational plus structural)
11. "Zizimin2 and zizimin1 have similar primary structures and both proteins bound and activated Cdc42 but not the Cdc42-related proteins TC10 or TCL." (PMID: 15710388, in vitro)
12. "Anemia and aberrant erythrocyte morphologic features were recapitulated in a newly generated dock11-knockout zebrafish model" (PMID: 37342957, model organism)
13. "Ziz2 KO mice had a higher percentage of early bone marrow B cells (Fraction A), but a reduced fraction of marginal zone (MZ) B cells" (PMID: 25729399, model organism)
14. "cdc-42 and the guanine nucleotide exchange factor dock-11 are also required for branch formation." (PMID: 41278672, model organism)

15. "we show that the protein expression of Zizimin2, which is also restricted to lymphoid tissues and lymphocytes, is reduced in aged mice" (PMID: 22494997, model organism; conflicts with human GTEx and HPA)
16. "DOCK11 deficiency is a multisystem autoinflammatory disease that may present as acute liver failure." (PMID: 40107756, human clinical)
17. "In most cases, the severity of the conditions necessitates allogeneic marrow transplantation as a treatm[ent]" (PMID: 39644982, review)
18. "Diagnosis should be considered primarily when encountering an early-onset autoinflammatory skin and digestive disorder, along with a primary immunodeficiency and either thrombocytopenia or a bleeding tendency" (PMID: 39644982, review)
19. "The complete pathophysiology of these diseases is not yet fully understood, and further studies are required to elucidate the underlying mechanisms, which could guide therapeutic choices" (PMID: 39644982, review)

Hypothesis status

✔ **Supported.** Hemizygous DOCK11 loss of function causes ADMIDX through failed CDC42 activation. DOCK11 works as a membrane-dependent positive-feedback switch, which explains why hypomorphic missense alleles are as damaging as nulls. gnomAD hemizygous pLoF carriers truncate earlier in the open reading frame than disease alleles ($p = 0.0137$), which reconciles population data with complete penetrance. Allele class associates with the dominant clinical axis (Fisher $p = 0.035$, suggestive). Allogeneic HSCT is the only curative treatment reported.

✘ **Refuted.** Immune-restricted disease does not reflect immune-restricted DOCK11 expression. GTEx and HPA show broad expression, confirmed independently by the cryo-EM paper. The mouse lymphoid-restriction claim does not transfer to human.

✘ **Negative result.** The IMPC primary phenotyping screen on hemizygous Dock11 knockout mice returned only increased kidney weight, with no immune call.

? **Open.** Whether a clean null allele is milder than a DOCKER-truncating allele (the dead-end-scaffold prediction). Whether GEF redundancy by DOCK9, DOCK10 or others accounts for non-haematopoietic sparing. Whether the erythroid phenotype is cell-intrinsic to human erythroblasts. What nuclear DOCK11 does. Whether calcineurin or JAK inhibition works clinically in this disease.

Limitations and knowledge gaps

⚠ **Sample size dominates every number.** Thirteen patients from 12 families, published 2023-2025, plus isolated later cases. HPO denominators are 1 to 12. Anisocytosis at 4/4 has a Wilson lower bound of 51%, so the data cannot distinguish a universal feature from a common one. No frequency in this report should be quoted as a population estimate.

⚠ **The genotype-phenotype split is weak evidence.** The assignment of patients to axes comes from a published group-level re-evaluation, not per-patient chart data. One cell is zero, so the odds ratio is uninformative. The two index cohorts were ascertained differently, which is an uncontrolled confounder: one was recruited through autoimmunity, the other through systemic inflammation and anaemia.

⚠ **The positional gnomAD analysis compares five disease alleles against 23 population alleles.** Five is a small numerator for a Mann-Whitney test. LOFTEE misannotation is an alternative explanation the data cannot exclude, and gnomAD independently depletes severe paediatric disease.

⚠ **No outcome data of any kind.** No survival analysis, life expectancy, mortality rate, quality-of-life instrument, HSCT outcome series, interventional trial, registry or natural history study. Section 11 is qualitative by necessity.

⚠ **The structural mechanism is a model applied to patient variants, not a test of them.** The cryo-EM work used wild-type DOCK11 with engineered CDC42 mutants. No patient variant has been placed in these structures experimentally or assayed for exchange activity in the membrane-dependent system.

⚠ **Redundancy is inferred.** No experiment has shown that DOCK9 or DOCK10 compensates for DOCK11 in non-haematopoietic tissue. That inference carries the weight of the HSCT rationale.

⚠ **Model coverage is partial.** No animal model reproduces the autoantibody autoimmunity or the colitis. No iPSC or organoid model exists. The erythroid mechanism rests entirely on zebrafish.

⚠ **Variant interpretation is immature.** ClinVar holds 173 VUS against 7 DOCK11-specific P/LP small variants, and the eight published disease-causing missense alleles are not deposited with P/LP status. Clinical laboratories will return VUS for most DOCK11 missense findings.

Not available for this disease: Orphanet code, specific ICD-10 and ICD-11 codes, MeSH descriptor, prevalence and incidence figures, modifier genes, epigenetic signature, metabolomic or lipidomic signature, single-cell or spatial data, CRISPR screen data, naturally occurring disease in any other species (OMIA), breed associations (VBO), newborn screening, registered clinical trials.

Proposed follow-up experiments and actions

Test the dead-end-scaffold prediction. Express each patient truncation (p.Gln1252Ter, p.Leu1299fs, p.Ile1464fs, p.Ser1793fs, p.Tyr2012Ter) and a true early null in a DOCK11-knockout haematopoietic line. Measure protein stability, plasma membrane localisation by TIRF microscopy and CDC42-GTP loading by pulldown. The prediction is that C-terminal truncations localise normally but give lower CDC42-GTP than an early null, because they occupy the site without catalysing. A clean refutation would be equal CDC42-GTP across all alleles.

Measure the threshold directly. Titrate DOCK11 expression in a degron or inducible system from 0% to 100% of wild-type and read out CDC42-GTP, filopodium number and confined-channel migration speed. The feedback model predicts a sigmoid with a sharp transition, not a straight line. This is the single most informative experiment for explaining why missense equals null clinically.

Test the redundancy hypothesis. Knock out DOCK9 and DOCK10 singly and together in DOCK11-null fibroblasts or adipocytes and ask whether CDC42-GTP and filopodia collapse only on combined loss. If so, redundancy is demonstrated rather than inferred, which secures the HSCT rationale.

Resolve the erythroid branch in human cells. Differentiate DOCK11-knockout human CD34+ cells to erythroblasts and assay enucleation, membrane deformability by ektacytometry and cytoskeletal architecture. The zebrafish result needs a human cell-intrinsic counterpart before anisopoikilocytosis can be called a direct consequence.

Build a patient registry. Prospective collection of 30 or more DOCK11 patients with standardised allele-class assignment, residual protein quantification by immunoblot, organ-by-organ outcome and HSCT results. That is the only route to testing the genotype-phenotype split properly and to any survival estimate.

Standardise the functional assay panel for VUS resolution. Define and validate the CDC42-GTP pulldown, filopodium count and Treg FOXP3/IKZF2 flow panel against a set of known-pathogenic and known-benign DOCK11 alleles, so that PS3 and BS3 can be applied consistently. With 173 VUS already in ClinVar, this is the highest-yield diagnostic action.

Trial the mechanism-matched drugs. The NFATc1 hyperactivation result predicts calcineurin inhibitor benefit in the autoinflammatory axis; the impaired IL-2 to STAT5B result predicts JAK inhibitor or low-dose IL-2 benefit in the Treg-failure axis. Given 13 patients, an n-of-1 or basket design with molecular readouts (NFATc1 translocation, Treg FOXP3) is the realistic format.

Place a patient variant in the structure. Cryo-EM or structure prediction of a DOCKER-truncated DOCK11 with CDC42, combined with the membrane-dependent exchange assay from PMID: 42837459, would convert the threshold model from an inference about variant position into a measurement.

→ **Immediate clinical actions that need no new data.** Add DOCK11 to all primary immunodeficiency and autoinflammatory gene panels. Flag live vaccine contraindication at the point of genetic diagnosis. Measure residual DOCK11 protein in every new patient, because allele class is currently the only available prognostic marker. Consider HSCT assessment early in patients with expression-null alleles.

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