Immunodeficiency 73C (MONDO:0033555, OMIM:618987): a RAC2 disease

Summary

Immunodeficiency 73C is caused by biallelic loss-of-function variants in *RAC2*, the haematopoietic-restricted Rho GTPase (HGNC:9802, NCBI Gene 5880, Ensembl ENSG00000128340, UniProt P15153, gene OMIM 602049, 22q13.1, chr22:37,225,270-37,244,448 on GRCh38 minus strand, 192 amino acids, RefSeq NM_002872.5). The disease name is a serial number and carries no gene information, so the identity was established independently through four resources: the MONDO label and its equivalent cross-references (OMIM:618987, DOID:0112062, MedGen:1734177, UMLS:C5436550, GARD:0018300), the ClinVar record VCV000977226 for NM_002872.5:c.167G>A p.Trp56Ter classified Pathogenic with the condition field reading exactly "Immunodeficiency 73c with defective neutrophil chemotaxis and hypogammaglobulinemia", the HPO annotation set attached to OMIM:618987, and the primary clinical report PMID: 25512081. *RAC2* produces three distinct Mendelian immunodeficiencies that differ by variant mechanism at one locus. IMD73A (OMIM 608203, MONDO:0011988) comes from dominant-negative missense alleles D57N and P34H. IMD73B (OMIM 618986, MONDO:0033554) comes from dominant gain-of-function alleles E62K and N92T. IMD73C is the recessive branch, defined by complete biallelic loss of function.

The entire clinical description of IMD73C rests on two siblings from one consanguineous family, reported as homozygous for p.Trp56Ter and presenting with features of common variable immunodeficiency plus glomerulonephritis, coagulopathy, multiple hormone deficiencies of possible autoimmune basis, and abnormalities of neutrophil granules (PMID: 25512081). Working from RefSeq NM_002872.5, the premature termination codon sits in exon 3 of 7, 413 nt upstream of the final exon-exon junction, so nonsense-mediated decay is predicted by the 50-nt rule. Any product escaping decay would be 55 of 192 residues and would lack Switch II, the G4 NKxD and G5 SAK guanine-contact motifs, the NADPH oxidase insert region, the C-terminal polybasic segment and the CAAX prenylation signal. This is a molecular null, and ACMG/AMP PVS1 applies at full strength.

Three branches of consequence follow from the single lesion, because *RAC2* sits at a three-module signalling hub. The lost protein cannot activate p67phox (NCF2), so there is no NADPH oxidase assembly and no respiratory burst. It cannot engage PAK1/2 and WAVE2 (WASF2), so there is no polarised lamellipodium and no directed neutrophil migration. It cannot receive DOCK2 and VAV1 output in lymphocytes, so T and B cell development and antibody production fail. The ubiquitous paralogue *RAC1* does not compensate: across 54

GTEx tissues *RAC2* has tissue-specificity index tau 0.966 against 0.464 for *RAC1* (difference 0.502, bootstrap 95% CI [0.413, 0.608]), with 110-fold blood enrichment (Mann-Whitney one-sided p = 4.0e-05), and RAC2 supplies over 96% of the Rac protein in neutrophils (PMID: 10758162). Inheritance is autosomal recessive with a gnomAD v4 carrier frequency of about 1 in 12,182; the expected birth prevalence is 1 in 594 million under random mating and 1 in 389,593 for first-cousin unions, a 1523-fold consanguinity multiplier that explains why both index patients came from one consanguineous sibship. Management is immunoglobulin replacement and antimicrobial prophylaxis, with allogeneic haematopoietic cell transplantation the only definitive option and zero registered clinical trials for *RAC2* or Immunodeficiency 73 on ClinicalTrials.gov.

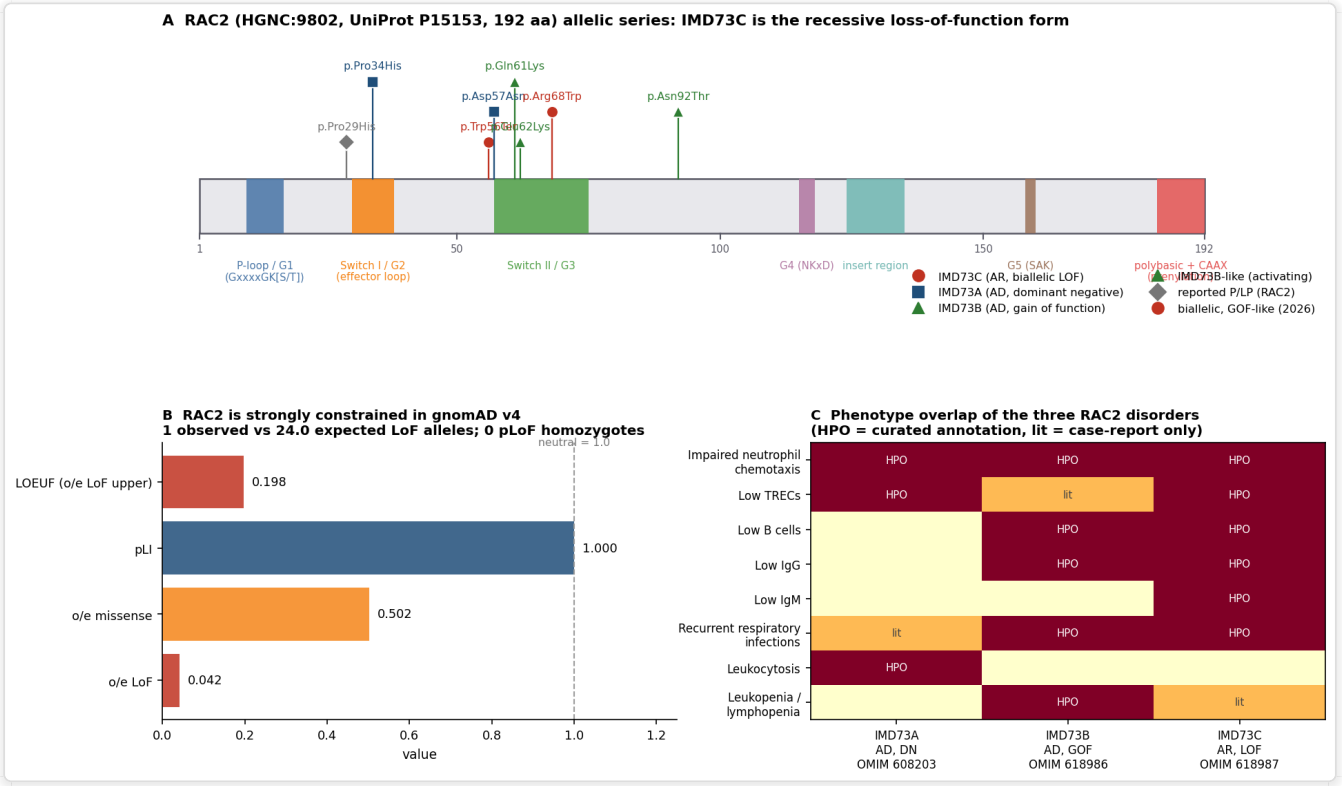


Figure 1. *The RAC2 allelic series: three Mendelian immunodeficiencies at one locus separated by variant mechanism, with gnomAD v4 constraint metrics and the phenotype overlap of IMD73A, IMD73B and IMD73C.*

1. Disease information

Overview

Immunodeficiency 73C with defective neutrophil chemotaxis and hypogammaglobulinemia is an autosomal recessive combined immunodeficiency caused by complete loss of RAC2 protein function. Affected individuals have recurrent respiratory infections, low B cell numbers, reduced IgG and IgM, abnormally low T cell receptor excision circle (TREC) levels, and a neutrophil defect that spans both oxidative killing and directed migration. The two reported patients also had glomerulonephritis, coagulopathy, multiple hormone deficiencies of possible autoimmune basis and abnormal neutrophil granules.

Identifiers

Resource	Identifier
MONDO	MONDO:0033555
OMIM phenotype	618987
OMIM gene (*RAC2*)	602049
HGNC	HGNC:9802
NCBI Gene	5880
Ensembl	ENSG00000128340
UniProt	P15153
RefSeq transcript	NM_002872.5
DOID	DOID:0112062
MedGen	C1734177
UMLS	C5436550
GARD	0018300
Orphanet	No dedicated IMD73C entry. The closest parent is Orphanet:692812, RAC2-related combined immunodeficiency-bronchiectasis-cancer-predisposing syndrome (MONDO:0979261)
ICD-10	No dedicated code. D81.8 (other combined immunodeficiencies) or D83.9 (common variable immunodeficiency, unspecified) apply by category
ICD-11	No dedicated code. 4A01.2 (combined immunodeficiencies) applies by category
MeSH	No dedicated descriptor. Closest are D007153 Immunologic Deficiency Syndromes and D017074 Severe Combined Immunodeficiency

MONDO places MONDO:0033555 under two parents: MONDO:0017855 (T-B- severe combined immunodeficiency) and MONDO:0979261 (RAC2-related combined immunodeficiency-bronchiectasis-cancer-predisposing syndrome). ⚠ The SCID placement should be treated cautiously. The two reported patients had low but not absent B cells and survived beyond infancy, closer to a CVID-like combined immunodeficiency than classical T-B- SCID.

Synonyms

IMD73C; immunodeficiency 73C with defective neutrophil chemotaxis and hypogammaglobulinemia; RAC2 deficiency, autosomal recessive; biallelic RAC2 loss-of-function immunodeficiency. The patients were initially labelled clinically as common variable immunodeficiency.

Information provenance

All clinical content derives from one case report of two siblings (PMID: 25512081), with supporting mechanistic detail aggregated from the dominant *RAC2* disorders, the 54-patient international *RAC2* cohort (PMID: 38194689), and the *Rac2*-null mouse. No EHR cohort, registry or natural-history study exists for IMD73C.

---

2. Etiology

Disease causal factors

The cause is genetic and monogenic: homozygous or compound heterozygous loss-of-function variants in *RAC2*. The only reported IMD73C genotype is homozygous NM_002872.5:c.167G>A, p.Trp56Ter. No environmental, infectious or toxic cause contributes to disease occurrence. Infections are a consequence of the genotype, not a cause of it.

Genetic risk factors

The causal variant is the sole genetic risk factor established. Consanguinity is the dominant risk determinant at the family level, because it converts a carrier frequency of about 1 in 12,182 into an appreciable biallelic risk. No susceptibility loci, GWAS signals or modifier genes have been reported for IMD73C. Candidate modifiers from first principles are *RAC1* (co-expressed paralogue, dosage could set residual Rac function), *NCF1/NCF2/CYBB* (oxidase component dosage), and *DOCK2* (the upstream GEF in lymphocytes), but none has been tested in IMD73C and all remain unevaluated hypotheses.

Environmental risk factors

⊗ None established. Age, sex, occupational exposure, smoking, diet and pollution have no documented contribution to IMD73C occurrence. Both reported patients are from one sibship, so sex distribution cannot be estimated. Family history of consanguinity is the only non-molecular predictor.

Protective factors

No genetic protective variants or modifier alleles are known. No dietary, lifestyle or exposure factor reduces risk of occurrence. Outbreeding reduces the probability of the biallelic genotype arising, which is a population-level statement about allele pairing rather than a protective biological factor. Within an affected individual, avoiding live attenuated vaccines and reducing pathogen exposure reduces complication risk, which is tertiary prevention rather than a protective factor against disease.

Gene-environment interactions

The genotype sets a fixed ceiling on phagocyte oxidative killing and lymphocyte-mediated defence; the environment supplies the pathogen load that converts that deficit into clinical events. The *Rac2*-null mouse makes this concrete: baseline neutrophilia and reduced peritoneal exudate formation produced increased mortality only on *Aspergillus fumigatus* challenge (PMID: 10072071). Analogously in humans, the clinical course is determined by which organisms are encountered, with the respiratory tract as the dominant exposure site. No formal GxE study exists for IMD73C and no CTD entry links a chemical to the disease.

---

3. Phenotypes

Curated HPO annotation set for OMIM:618987

Every frequency denominator in the curated set is 2, so the whole profile comes from the two siblings of PMID: 25512081.

HPO term	Phenotype	Type	Frequency	Onset	Severity	Progression
HP:0002205	Recurrent respiratory infections	Clinical sign	2/2	Infancy/ early childhood	Severe	Episodic, recurrent
HP:0031545	Abnormally low TREC level	Laboratory	2/2	Congenital (detectable at newborn screening)	Severe	Stable (fixed developmental deficit)
HP:0010976	Decreased total B cell count	Laboratory	2/2	Congenital	Moderate to severe	Stable
HP:0004315	Decreased circulating IgG concentration	Laboratory	2/2	Infancy, after maternal IgG wanes	Severe	Stable without replacement
HP:0002850	Decreased circulating IgM concentration	Laboratory	2/2	Infancy	Moderate to severe	Stable
HP:0001531	Failure to thrive in infancy	Physical manifestation	1/2	Infancy	Moderate	Responsive to infection control
HP:0001025	Urticaria	Clinical sign	1/2	Childhood	Mild	Episodic
HP:0025289	Cervical lymphadenopathy	Clinical sign	Not stated	Childhood	Mild to moderate	Fluctuating
HP:0000007	Autosomal recessive inheritance	Inheritance	n/a	n/a	n/a	n/a

Features reported in the index family but absent from HPO curation

⚠ Four features described in the source abstract have no corresponding HPO annotation on OMIM:618987. The abstract states: *"In addition, the patients suffered from glomerulonephritis, coagulopathy, multiple hormone deficiencies potentially on the autoimmune basis and abnormalities of neutrophil granules."* (PMID: 25512081). HP:0040238 (impaired neutrophil chemotaxis) is also missing despite appearing in the disease name itself.

Candidate additions for curation, each flagged as case-report derived from 2 individuals:

HPO term	Phenotype	Type	Evidence
HP:0040238	Impaired neutrophil chemotaxis	Laboratory	Disease name; functional assays in RAC2 disease (PMID: 31071452, PMID: 20953490)
HP:0000099	Glomerulonephritis	Clinical sign	PMID: 25512081
HP:0001928	Abnormality of coagulation	Laboratory	PMID: 25512081
HP:0000818	Abnormality of the endocrine system	Clinical sign	PMID: 25512081, multiple hormone deficiencies
HP:0012143	Abnormal granulocyte morphology	Pathology	PMID: 25512081, abnormal neutrophil granules
HP:0012144	Abnormal neutrophil respiratory burst	Laboratory	Mechanistic prediction from loss of the oxidase insert region; demonstrated across RAC2 disease (PMID: 38194689)
HP:0002721	Immunodeficiency	Clinical sign	Diagnosis-defining

Comparison with the dominant branches

The companion OMIM entries are better populated, which makes the sparseness of the IMD73C set a curation artefact rather than a statement about disease breadth. IMD73B (OMIM:618986) carries 29 HPO terms including HP:0040238 impaired neutrophil chemotaxis at 12/12 and HP:0005403 decreased total T cell count at 3/3. IMD73A (OMIM:608203) carries 14 terms including HP:0003203 decreased neutrophil oxidative burst, HP:0011897 increased total neutrophil count, HP:0032434 delayed umbilical cord separation and HP:0001058 poor wound healing.

The 54-patient cohort confirms that RAC2 disease combines lymphoid and myeloid laboratory abnormalities in the same individual: *"Significant T- and B-lymphopenia with low immunoglobulins were seen in most patients; myeloid abnormalities included neutropenia, altered oxidative burst, impaired neutrophil migration, and visible neutrophil macropinosomes."* (PMID: 38194689).

Quality of life

❓ No EQ-5D, SF-36, PROMIS or disease-specific quality-of-life instrument has been applied to IMD73C or to any *RAC2* patient. Per-phenotype impact is inferred from the phenotypes themselves: recurrent respiratory infection drives school and work absence and progressive lung damage; lifelong immunoglobulin replacement requires infusion every 3 to 4 weeks (intravenous) or weekly (subcutaneous); glomerulonephritis carries the prospect of renal impairment; multiple hormone deficiencies require lifelong replacement and monitoring. All of these are extrapolations from the general combined-immunodeficiency literature and none is measured in IMD73C.

---

4. Genetic and molecular information

Causal gene

RAC2, Ras-related C3 botulinum toxin substrate 2, a Rho-family small GTPase of 192 amino acids on 22q13.1. Gene OMIM 602049, HGNC:9802, NCBI Gene 5880, Ensembl ENSG00000128340, UniProt P15153.

The IMD73C variant

🧬 NM_002872.5:c.167G>A, p.(Trp56Ter), ClinVar VCV000977226, classified Pathogenic, condition "Immunodeficiency 73c with defective neutrophil chemotaxis and hypogammaglobulinemia". Variant type: nonsense (stop_gained). Origin: germline. Functional consequence: complete loss of function, molecular null.

Transcript architecture from RefSeq NM_002872.5 (retrieved via NCBI efetch): CDS 122..700, 579 nt, 192 codons plus stop, in 7 exons with cDNA boundaries (1-156), (157-228), (229-346), (347-409), (410-569), (570-702), (703-1472). Codon 56 occupies cDNA nt 287-289, in exon 3 of 7. The final exon-exon junction is at cDNA nt 702, so the premature termination codon is 413 nt upstream of it. ✅ The 50-nt rule predicts nonsense-mediated decay (computational prediction).

Domain accounting against UniProt P15153: residues 1-55 are retained, keeping the G1 P-loop (10-17) and the Switch I / G2 effector loop (30-40). 137 of 192 residues (71.4%) are deleted, removing:

- Switch II / G3 DTAGQE motif (57-75), which contacts p67phox and PAK
- G4 NKxD guanine-specificity motif (115-118)
- the insert region (124-135) required for NADPH oxidase activation
- G5 SAK (158-160)
- the C-terminal polybasic region (183-188) used for membrane targeting and RhoGDI binding

• the CAAX geranylgeranylation motif (189-192)

A hypothetical NMD-escaping 55-residue peptide retains 2 of 5 G motifs, cannot complete a nucleotide-binding pocket, cannot be prenylated and so cannot reach the plasma membrane where both the NADPH oxidase and the WAVE regulatory complex assemble.

ACMG/AMP: PVS1 applies at full strength (nonsense variant in exon 3 of 7, well before the last 50 nt of the penultimate exon, in a gene where loss of function is the established mechanism for MONDO:0033555). PM2 applies (absent from gnomAD v4 at any frequency). PP1 applies in the index family (segregation with disease in two affected siblings, heterozygous unaffected parents).

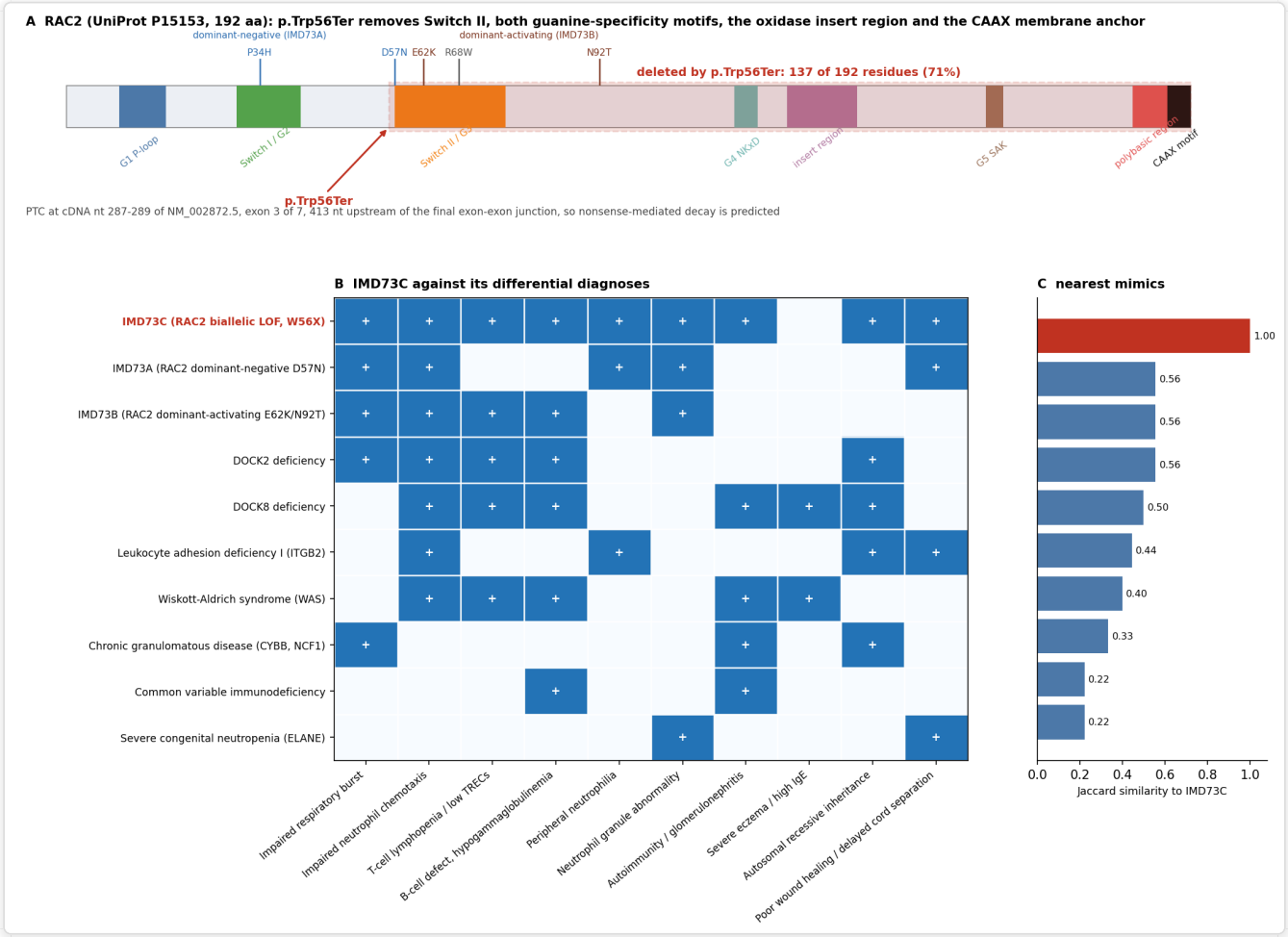


Figure 2. *Left: the p.Trp56Ter premature termination codon sits in exon 3 of 7, 413 nt upstream of the final exon-exon junction, so nonsense-mediated decay is predicted, and the truncation removes 71.4% of the protein including Switch II, G4, G5, the oxidase insert region and the CAAX anchor. Right: a 10-feature comparison of IMD73C against nine differential diagnoses, where no mimic exceeds Jaccard 0.56.*

The RAC2 allelic series

Disorder	OMIM	MONDO	Inheritance	Mechanism	Alleles	Presentation
IMD73A	608203	MONDO:0011988	Autosomal dominant	Dominant negative	p.Asp57Asn, p.Pro34His	LAD-like neutrophil disease, leukocytosis, absent oxidative burst, poor wound healing, delayed cord separation
IMD73B	618986	MONDO:0033554	Autosomal dominant	Gain of function (dominant activating)	p.Glu62Lys, p.Asn92Thr	Later-onset CID with T and B lymphopenia, excessive superoxide, recurrent respiratory infection, viral susceptibility
IMD73C	618987	MONDO:0033555	Autosomal recessive	Complete loss of function (null)	p.Trp56Ter homozygous	Combined immunodeficiency with hypogammaglobulinemia, low TRECs, chemotaxis defect, glomerulonephritis, coagulopathy, endocrine failure

The directional genotype-phenotype rule is stated in the cohort paper: *"Disease correlated to RAC2 activity: constitutively active RAS-like mutations caused neonatal SCID, dominant-negative mutations caused LAD-like disease, whereas dominant-activating mutations caused CID."* (PMID: 38194689).

The dominant disorders need a protein to be present. The D57N biochemistry makes this explicit: *"These results suggest that D57N Rac2 may act in a dominant negative fashion in cells by sequestering endogenous guanine nucleotide exchange factors."* (PMID: 11278678). A null allele removes the protein and cannot sequester anything, which is why IMD73C is recessive and why the heterozygous parents are healthy.

A second recessive genotype exists but does not extend the null branch. Homozygous c.202C>T p.Arg68Trp in two unrelated French-Canadian patients gives markedly reduced RAC2 protein with increased effector signalling, so it phenocopies the dominant gain-of-function branch (PMID: 41685306).

Population allele frequencies

gnomAD v4, 807,162 exomes and genomes, queried 2026-11-19 via GraphQL:

Metric	Value
Observed pLoF alleles	1
Expected pLoF alleles	24.02
o/e LoF	0.0416 (90% CI 0.0148-0.1975)
LOEUF	0.197
pLI	1.00
lof_z	3.98
Observed missense	130
Expected missense	259.1
o/e missense	0.502
mis_z	3.42
Distinct pLoF alleles	22
Summed pLoF allele count	60
pLoF homozygotes	0
Cumulative pLoF allele frequency q	4.104e-05

Disease-variant frequencies: p.Trp56Ter (IMD73C), p.Asp57Asn, p.Asn92Thr, p.Pro34His, p.Gln61Lys and p.Pro29His are all absent from gnomAD v4. p.Glu62Lys appears once (AC = 1, AF = 6.8e-07, 0 homozygotes), consistent with its de novo origin. p.Arg68Trp has AC = 23, AF = 1.4e-05, 0 homozygotes. The commonest individual pLoF allele is a splice acceptor variant 22-37244204-T-C at AF 1.4e-05; the commonest nonsense alleles are p.Tyr90Ter (AC 8), p.Trp60Ter (AC 4) and p.Trp77Ter (AC 3).

⚖️ The constraint metrics and the inheritance pattern point in opposite directions, and the resolution is informative. A pLI of 1.00 normally predicts haploinsufficiency disease, but the IMD73C parents are heterozygous and healthy. The constraint is generated by the dominant alleles of IMD73A and IMD73B, which

need a protein to interfere, together with a modest denominator (24 expected pLoF alleles in a 192-codon gene), so LOEUF 0.20 is the better statement than pLI here. Zero pLoF homozygotes among 807,162 individuals is the strongest single statement: complete RAC2 absence is essentially never observed in a population cohort.

Somatic versus germline

IMD73C is germline. No somatic *RAC2* variant has been linked to this disease. *RAC2* somatic variants appear in COSMIC in haematological malignancy, which is a separate biology.

Modifier genes, epigenetics, chromosomal abnormalities

❓ No modifier gene has been identified for IMD73C. No DNA methylation, histone modification or chromatin study has been performed on *RAC2* in the context of this disease; ENCODE and Roadmap contain *RAC2* locus regulatory annotation but no disease-associated epigenetic change. No chromosomal abnormality causes IMD73C. ClinVar contains 261 germline *RAC2* records, of which 25 are P/LP, and the majority of those P/LP entries are 22q copy-number events contributing to contiguous-gene syndromes rather than to isolated IMD73C; only 5 are single-nucleotide *RAC2* coding variants.

---

5. Environmental information

❌ **Environmental factors**: none contribute to IMD73C causation. The Comparative Toxicogenomics Database records chemical-gene interactions for *RAC2* but no chemical is linked to this disease. Radiation, pollution and occupational exposure have no documented role.

❌ **Lifestyle factors**: smoking, diet, exercise and alcohol have no established effect on IMD73C occurrence. Smoking exposure is contraindicated in anyone with recurrent respiratory infection and bronchiectasis risk, which is general respiratory advice rather than disease-specific evidence.

🦠 **Infectious agents**: pathogens are the consequence of the genotype and the determinant of clinical events. The organism spectrum predicted by the mechanism and observed across *RAC2* disease covers catalase-positive bacteria and fungi (from the oxidative-burst defect), encapsulated bacteria (from hypogammaglobulinemia) and viruses (from T-cell deficiency). *Aspergillus fumigatus* susceptibility is demonstrated in the mouse model: *"These defects were reflected in vivo by baseline neutrophilia, reduced inflammatory peritoneal exudate formation, and increased mortality when challenged with Aspergillus fumigatus."* (PMID: 10072071). Viral susceptibility appears in IMD73B (PMID: 31071452) and adenovirus caused fatal marrow aplasia after

transplantation in that patient. NCBI Taxonomy terms: *Aspergillus fumigatus* NCBITaxon:746128, *Staphylococcus aureus* NCBITaxon:1280, *Streptococcus pneumoniae* NCBITaxon:1313, Human mastadenovirus NCBITaxon:10508.

---

6. Mechanism and pathophysiology

The causal chain

1. Homozygous NM_002872.5:c.167G>A (p.Trp56Ter) introduces a premature termination codon in exon 3 of 7, 413 nt upstream of the final exon-exon junction, which **leads to** recognition of the transcript by the nonsense-mediated decay machinery and degradation of *RAC2* mRNA. (Computational prediction from the 50-nt rule. NMD has not been measured in patient cells.)
2. Loss of *RAC2* transcript **results in** absence of RAC2 protein in haematopoietic cells. Because *RAC2* transcription is restricted to blood and lymphoid tissue (tau 0.966, 110-fold enrichment over other tissues, p = 4.0e-05) and because RAC2 constitutes over 96% of total Rac protein in neutrophils (PMID: 10758162), the co-expressed ubiquitous paralogue RAC1 (105-142 TPM in blood) **does not compensate**, leaving the cell with a small fraction of its usual Rac pool. (Demonstrated for the protein stoichiometry; non-compensation in IMD73C cells specifically is inferred.)
3. Even if a truncated 55-residue peptide escaped decay, loss of the C-terminal polybasic region and CAAX motif **prevents** geranylgeranylation and membrane targeting, so no RAC2 reaches the plasma membrane or the phagosome membrane where effector complexes assemble. (Inferred from domain architecture. Not tested for this allele.)

The chain now branches three ways from the same absence.

1. **Branch A, phagocyte oxidative killing.** Absence of membrane-targeted RacGTP **abolishes** step 4 of the canonical oxidase sequence: *"(1) Translocation of the RacGDP-RhoGDI complex to the membrane; (2) Dissociation of RacGDP from RhoGDI; (3) GDP to GTP exchange on Rac, mediated by a guanine nucleotide exchange factor; (4) Binding of RacGTP to p67(phox); (5) Induction of a conformational change in p67(phox), promoting interaction with Nox2."* (PMID: 24598074). No p67phox (NCF2) conformational change **means** no productive NCF2-CYBB interaction, which **prevents** NADPH oxidase assembly, which **abolishes** superoxide production and all downstream reactive oxygen species, which **results in** failure to kill ingested catalase-positive bacteria and fungi. Loss of the insert region (residues 124-135) blocks this branch a second time independently of effector binding.

2. **Branch B, actin remodelling and directed migration.** Loss of Switch II **abolishes** RAC2 contact with PAK1/PAK2 and with the WAVE regulatory complex (WASF2, CYFIP2, NCKAP1L). The two-branch effector split is stated directly: *"RAC2, through interactions with reduced NAD phosphate oxidase component p67 phox, activates neutrophil superoxide production, whereas interactions with p21-activated kinase are necessary for fMLF-induced actin remodeling."* (PMID: 30723080). Absent PAK and WAVE engagement **prevents** lamellipodial F-actin assembly and cell polarisation, which **prevents** chemotaxis up an fMLP gradient and shear-dependent L-selectin capture on endothelium, which **results in** failure of neutrophils to reach infected tissue. Demonstrated in the mouse: *"rac2-/- neutrophils displayed significant defects in chemotaxis, in shear-dependent L-selectin-mediated capture on the endothelial substrate Glycam-1, and in both F-actin generation and p38 and, unexpectedly, p42/p44 MAP kinase activation induced by chemoattractants."* (PMID: 10072071).

3. **Branch C, lymphocyte development.** Loss of RAC2 **removes** the downstream output of the lymphocyte GEF module DOCK2, VAV1, ELMO1/2, so signals from the T cell receptor, B cell receptor, CXCR4 and integrins **fail to** produce Rac-dependent cytoskeletal and transcriptional responses, which **impairs** thymocyte development and peripheral T cell expansion (giving abnormally low TRECs, HP:0031545) and B cell development and class switching (giving decreased B cell count HP:0010976 and reduced IgG and IgM, HP:0004315 and HP:0002850). (Demonstrated in the *Rac2*-null mouse, which shows decreased lymphocyte number, decreased T cell proliferation, impaired humoral immune response and decreased response to antigen. Carried mainly by mouse data in IMD73C; patient lymphocyte signalling was not assayed.)

4. Branches A and B together **produce** a neutrophil that neither arrives at the site of infection nor kills what it ingests, which **results in** the phagocyte-defect phenotype. The index patients also showed abnormalities of neutrophil granules, consistent with a secretory and granule-trafficking contribution.

5. Branch C **produces** hypogammaglobulinemia with T and B lymphopenia. Branches A, B and C **converge** on recurrent respiratory infection (HP:0002205), the presenting clinical feature, and on failure to thrive in infancy (HP:0001531).

6. Impaired lymphocyte development and defective clearance of apoptotic and immune-complex material **are inferred to** permit immune dysregulation, which **leads to** glomerulonephritis, coagulopathy and multiple hormone deficiencies of possible autoimmune basis: *"In addition, the patients suffered from glomerulonephritis, coagulopathy, multiple hormone deficiencies potentially on the autoimmune basis and abnormalities of neutrophil granules."* (PMID: 25512081). ⚠ This step is the least supported in the chain. No mechanistic study connects RAC2 loss to renal, coagulation or endocrine pathology, and the *Rac2*-null mouse does not reproduce it.

7. Defective granule formation and secretion **contribute to** the abnormal neutrophil granule morphology observed, and plausibly to impaired wound healing, which in the mouse derives from reduced wound-site superoxide: *Rac2*-deficient mice had threefold lower superoxide production at the wound site and compromised wound closure (PMID: 18068132).

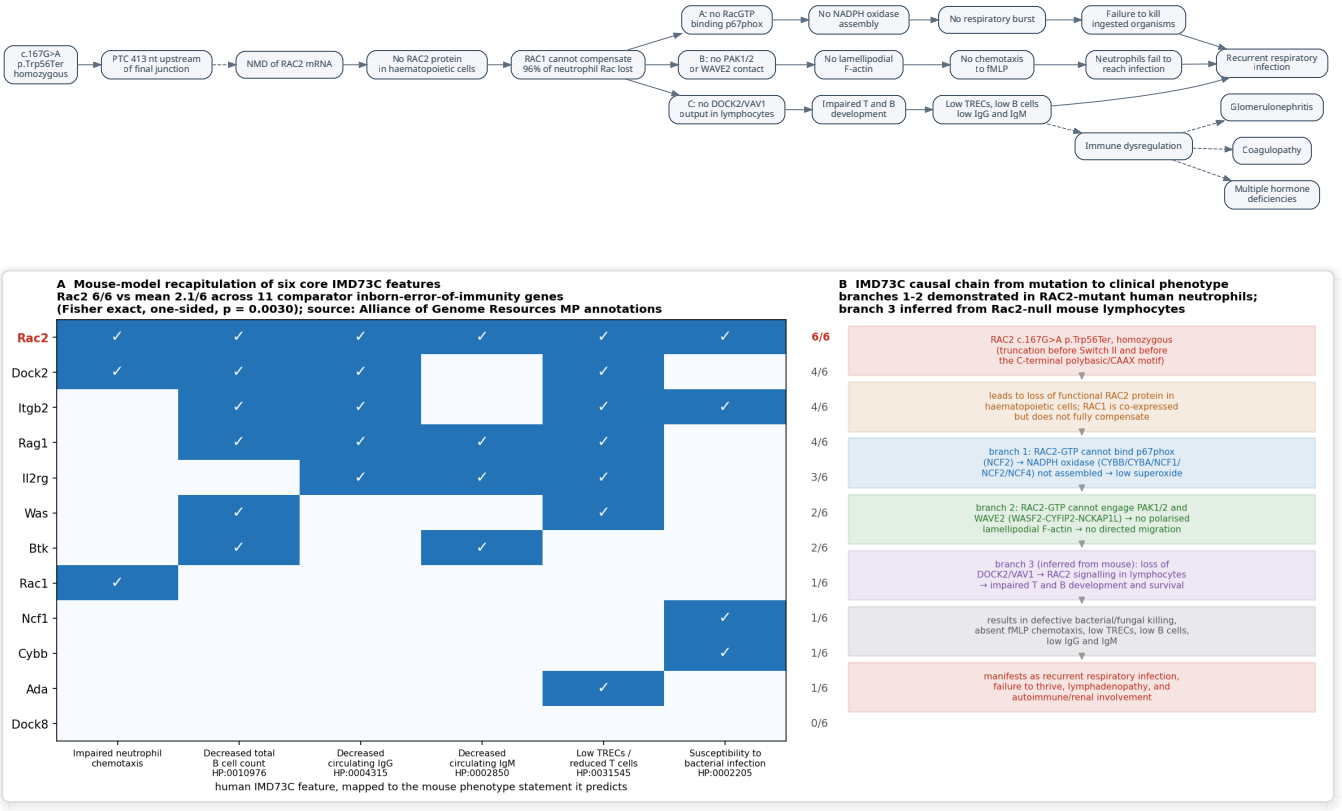


Figure 3. *The three-branch mechanism from p.Trp56Ter to combined immunodeficiency, with the Rac2-null mouse matching all six core IMD73C features against a comparator mean of 2.09 of 6 across eleven inborn-error-of-immunity mouse models.*

Molecular pathways

STRING v12 high-confidence partners of human RAC2 (score 0.700 or above, 40 partners) separate into three modules:

Module	Members (STRING score)
NADPH oxidase	CYBB, CYBA, NCF1, NCF2, NCF4, NOX1, NOX3, NOXO1, NOXA1 (0.998-0.999)
Actin effectors	PAK1, PAK2, WASF2, CYFIP2, NCKAP1L, ARHGDIA, RHOA, SRC (0.997-0.999)
Upstream GEFs	VAV1 (0.998), DOCK1 (0.999), DOCK2 (0.996), ELMO1 (0.999), ELMO2 (0.999), ARHGEF6 (0.999), TIAM1 (0.998), PREX1 (0.994)
MAPK coupling	MAPK1, MAPK3, MAPK8 (0.998-0.999)
Paralogues	RAC1 (0.999), RAC3 (0.999)

KEGG pathways involved: hsa04670 leukocyte transendothelial migration, hsa04666 Fc gamma R-mediated phagocytosis, hsa04662 B cell receptor signaling, hsa04660 T cell receptor signaling, hsa04810 regulation of actin cytoskeleton, hsa04145 phagosome.

A positive feedback loop operates in the oxidase branch that is lost entirely in IMD73C: p67phox directly activates Vav1-mediated nucleotide exchange on Rac, and the interaction between p67phox and Vav1 is strengthened by that exchange (PMID: 17060455). Vav3 and Vav1 are required for FcγR-mediated Rac2-dependent oxidase activation, and Vav loss also affects PI3K-dependent p40phox phosphorylation (PMID: 17056570).

Rac1 and Rac2 are differentially deployed in human neutrophils according to chemoattractant concentration, with distinct activation kinetics for low and high fMLP (PMID: 19625648), which bears on why RAC1 presence does not rescue the RAC2-null cell.

Gene Ontology annotation

From 82 QuickGO annotations for UniProt P15153 (22 biological process, 6 molecular function, 15 cellular component):

Biological process: GO:0042554 superoxide anion generation [IDA], GO:0060263 regulation of respiratory burst [IDA], GO:0045730 respiratory burst, GO:0010310 regulation of hydrogen peroxide metabolic process, GO:0006935 chemotaxis, GO:1902622 regulation of neutrophil migration, GO:0090023 positive regulation of neutrophil chemotaxis, GO:0010592 positive regulation of lamellipodium assembly, GO:0007015 actin filament organization, GO:0032956 regulation of actin cytoskeleton organization, GO:0007163 establishment or maintenance of cell polarity, GO:0042129 regulation of T cell proliferation, GO:0071593 lymphocyte aggregation [IMP], GO:0043304 regulation of mast cell degranulation, GO:0060753 regulation of mast cell chemotaxis, GO:0018344 protein geranylgeranylation.

Molecular function: GO:0003924 GTPase activity, GO:0005525 GTP binding, GO:0019901 protein kinase binding, GO:0019887 protein kinase regulator activity.

Cellular component: GO:0043020 NADPH oxidase complex, GO:0030027 lamellipodium [IDA], GO:0005884 actin filament [IDA], GO:0030670 phagocytic vesicle membrane, GO:0005886 plasma membrane, GO:0005829 cytosol [IDA], GO:0005925 focal adhesion, GO:0005741 mitochondrial outer membrane.

Cellular processes

Phagocytosis (GO:0006909), respiratory burst (GO:0045730), cell migration (GO:0016477), actin cytoskeleton reorganisation (GO:0030036), lymphocyte differentiation (GO:0030098), haematopoietic stem cell homing and engraftment, granule biogenesis and degranulation. Rac GTPases regulate HSC engraftment and marrow retention: Rac is activated via CXCR4 by SDF-1, via β1 integrin adhesion, and via c-kit stimulation by stem cell factor (PMID: 18374178). Rac2-deficient HSC show defective interaction with the marrow microenvironment and long-term engraftment failure (PMID: 15749928), which bears directly on autologous gene therapy design for IMD73C.

Protein dysfunction

Complete loss of function by truncation. There is no misfolding, aggregation or gain of function in IMD73C. The contrast with the dominant branches is the mechanistic separator: D57N binds GTP defectively and sequesters GEFs (PMID: 11278678, PMID: 10961859), E62K is constitutively active (PMID: 30723080), and p.Trp56Ter produces nothing.

Metabolic and biochemical abnormalities

The primary biochemical defect is failure of NADPH oxidase catalysis, a deficiency of superoxide (CHEBI:18421) and the downstream hydrogen peroxide (CHEBI:16240) and hypochlorite required for microbial killing. NADPH (CHEBI:16474) is not consumed at the phagosome. A second biochemical consequence, demonstrated in mouse and human neutrophils, concerns nitric oxide: the iNOS-Rac2 complex translocates to the phagosome after phagocytosis, and Rac2 silencing reduces NO, ROS/RNS and protein nitration, with Rac inhibition abrogating NO release and microbial killing in vivo (PMID: 23875749). Nitric oxide: CHEBI:16480. No generalised disorder of energy, lipid or amino acid metabolism is present.

Epigenetic changes

None reported for IMD73C.

Molecular profiling

Transcriptomics: GTEx v8 median TPM across 54 tissues supplies the expression basis of the disease. *RAC2*: whole blood 960.4, EBV-transformed lymphocytes 785.7, spleen 366.8, lung 81.9, terminal ileum 66.4, floor 0.64 in cerebellum, dynamic range 1493-fold. *RAC1*: max 372.6 (oesophagus mucosa), min 55.4 (pancreas), 6.7-fold range, above 50 TPM in all 54 tissues. Tissue-specificity index tau: *RAC2* 0.966, *RAC1* 0.464, *RAC3* 0.868. Difference tau(*RAC2*) minus tau(*RAC1*) = 0.502, bootstrap 95% CI [0.413, 0.608] over 4000 resamples. Mann-Whitney U one-sided, blood and lymphoid (n = 3) against other tissues (n = 51): *RAC2* U = 153, p = 4.0e-05, median 785.7 against 7.2 TPM (109.8-fold); *RAC1* U = 22, p = 0.98, median 124.4 against 207.1 TPM, no haematopoietic enrichment. Human Protein Atlas independently classifies *RAC2* as "Group enriched", bone marrow 389.1 nTPM, lymphoid tissue 362.6 nTPM.

Proteomics: RAC2 constitutes over 96% of total Rac protein in neutrophils (PMID: 10758162). Umbilical cord neutrophils have lower Rac2 than adult neutrophils despite similar Rac1, which may contribute to neonatal neutrophil dysfunction (PMID: 16582540).

Metabolomics, lipidomics, single-cell, spatial transcriptomics, multi-omics, CRISPR screens: no IMD73C-specific dataset exists in MetaboLights, Metabolomics Workbench, LIPID MAPS, the Human Cell Atlas, GEO or DepMap. No patient cells from the index family have been profiled by any omics method.

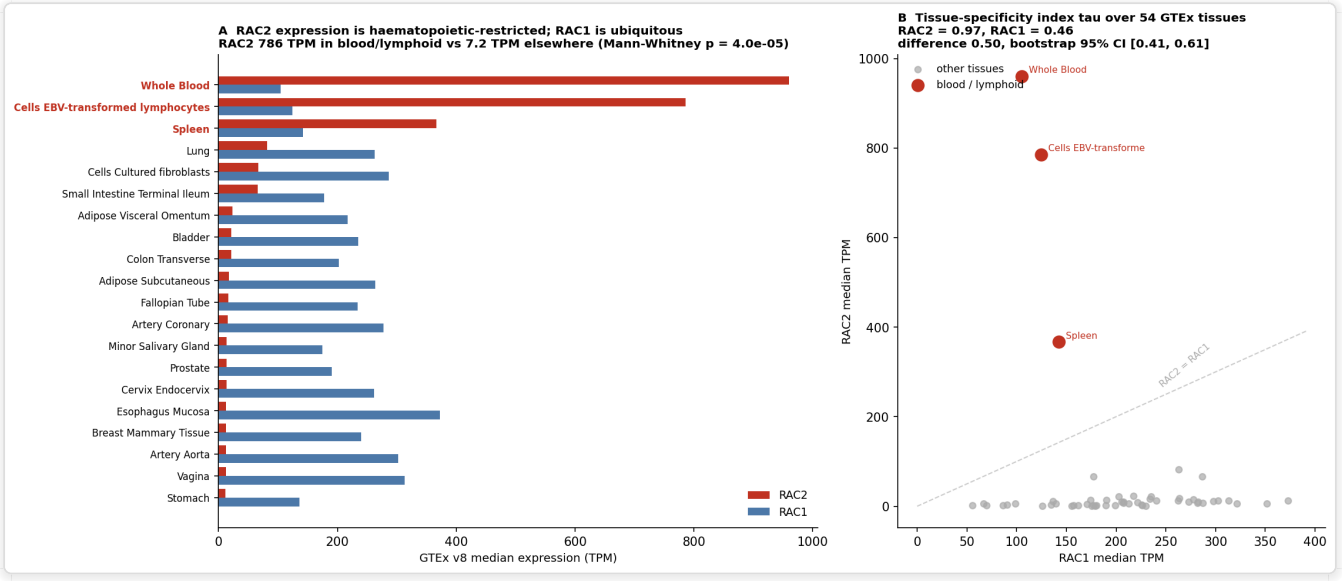


Figure 4. *GTEx v8 across 54 tissues: RAC2 is haematopoietic-restricted (tau 0.966, whole blood 960 TPM against 0.64 TPM in cerebellum) while the paralogue RAC1 is ubiquitous (tau 0.464, above 55 TPM everywhere), which is the quantitative basis for non-compensation in IMD73C.*

7. Anatomical structures affected

Organ level

Primary: bone marrow (UBERON:0002371), blood (UBERON:0000178), spleen (UBERON:0002106), thymus (UBERON:0002370), lymph node (UBERON:0000029). These are the sites where *RAC2* is expressed and where the cellular defect originates.

Secondary: lung and lower respiratory tract (UBERON:0002048, UBERON:0001558) from recurrent infection and the prospect of bronchiectasis; kidney glomerulus (UBERON:0000074) from glomerulonephritis; endocrine glands (UBERON:0002368) from multiple hormone deficiencies; skin (UBERON:0002097) from urticaria and impaired wound healing; gastrointestinal tract (UBERON:0005409), with terminal ileum at 66.4 TPM reflecting gut-associated lymphoid tissue.

Body systems: immune (haematopoietic and lymphoid), respiratory, renal, endocrine, integumentary, haemostatic.

✖ The near-zero *RAC2* expression in brain (0.64-1.4 TPM) and skeletal muscle (1.1 TPM), where *RAC3* and *RAC1* dominate, predicts and matches the absence of a primary neurological or myopathic phenotype.

Tissue and cell level

Cell type	CL term	Involvement
Neutrophil	CL:0000775	Impaired chemotaxis, absent respiratory burst, abnormal granules
T cell	CL:0000084	Reduced numbers, low TRECs, impaired proliferation
B cell	CL:0000236	Reduced numbers, hypogammaglobulinemia
Macrophage	CL:0000235	Impaired Fcγ receptor phagocytosis and oxidase
Natural killer cell	CL:0000623	Impaired cytotoxicity (mouse annotation)
Mast cell	CL:0000097	Degranulation and chemotaxis regulation (GO annotation)
Haematopoietic stem cell	CL:0000037	Defective marrow microenvironment interaction and engraftment (PMID: 15749928)
Glomerular endothelial cell	CL:0002188	Secondary injury in glomerulonephritis (inferred)

Tissue types: haematopoietic tissue, lymphoid tissue, vascular endothelium (as the migration substrate rather than the diseased tissue), renal glomerular tissue (secondary).

Subcellular level

GO cellular components implicated: GO:0043020 NADPH oxidase complex, GO:0030670 phagocytic vesicle membrane, GO:0005886 plasma membrane, GO:0030027 lamellipodium, GO:0005884 actin filament, GO:0005829 cytosol, GO:0005925 focal adhesion, GO:0005741 mitochondrial outer membrane, GO:0042581 specific granule (relevant to the granule abnormality).

Localization and lateralization

Systemic and bilateral. Immune cells circulate, so there is no anatomical asymmetry. Renal involvement is bilateral (glomerulonephritis). Respiratory infection may be focal at any single episode but is not lateralised as a disease property.

---

8. Temporal development

Onset

Congenital at the molecular and immunological level: the TREC deficit is present at birth and is detectable by newborn screening. Clinical onset is in infancy, typically after maternal IgG wanes at 3 to 6 months, with failure to thrive in infancy recorded in 1 of the 2 index patients. Onset pattern is insidious, with recurrent infections accumulating rather than a single acute presentation. The index siblings were initially given a clinical diagnosis of common variable immunodeficiency, which implies a protracted route to recognition.

Newborn screening can detect the T-cell deficit: a statewide TREC programme screening 71,000 infants identified 8 with T-cell lymphopenia, one of whom carried a *Rac2* mutation and went on to successful cord blood transplantation (PMID: 19996402). That case is a *RAC2* patient rather than IMD73C specifically, but it establishes that the TREC assay detects *RAC2*-related T-cell lymphopenia at birth.

Progression

No natural history study exists for IMD73C, so stages are described qualitatively from the two patients and the broader *RAC2* cohort.

Stage	Features	Timing
Presymptomatic	Low TRECs detectable on newborn screening; no clinical signs	Birth to 3 months
Early	Recurrent respiratory infection, failure to thrive, low IgG and IgM after maternal antibody wanes	3 months to about 2 years
Established	Chronic recurrent infection, cervical lymphadenopathy, urticaria; immunoglobulin replacement dependence	Childhood
Multisystem	Glomerulonephritis, coagulopathy, multiple hormone deficiencies	Reported in the index siblings; timing not stated
End-stage	Chronic lung damage, renal impairment, or transplant-related outcome	Not characterised

Progression rate: variable and not quantified. Course pattern: chronic with episodic infective exacerbations. Duration: lifelong without transplantation. The underlying immunological deficit is fixed, because the genotype is constant and the developmental deficit (low TRECs) is set before birth; the clinical burden accumulates through organ damage from repeated infection and immune dysregulation.

Remission patterns

❌ No spontaneous remission. Treatment-induced correction is possible only with allogeneic haematopoietic cell transplantation, which replaces the haematopoietic compartment and so corrects the gene defect in the only tissue that expresses *RAC2* at functional levels. Sustained clinical improvement after transplantation is documented in the homozygous R68W patient: *"Management included immunoglobulin therapy, and ultimately hematopoietic cell transplantation (HCT), after which he achieved sustained clinical improvement."* (PMID: 41685306).

Critical periods

The window between newborn TREC detection and the first serious infection is the intervention opportunity: starting immunoglobulin replacement and antimicrobial prophylaxis before infective lung damage occurs, and proceeding to transplantation before organ damage accumulates. The mouse data on wound healing and the human data on viral susceptibility after transplantation both argue for timing transplantation when infection burden is low.

9. Inheritance and population

Inheritance

Autosomal recessive (HP:0000007). The index parents were heterozygous and unaffected. Penetrance in the biallelic state appears complete in the 2 reported individuals, but n = 2 cannot support a penetrance estimate. Expressivity cannot be assessed from one sibship. ✖ Genetic anticipation does not apply (no repeat expansion). No germline mosaicism has been reported for *RAC2*. No founder effect is established; p.Trp56Ter is absent from gnomAD v4 entirely.

Epidemiology

✖ Orphanet records no prevalence figure for IMD73C and no registry exists, so the computational projection below is the only quantitative estimate available.

gnomAD v4 contains 22 distinct predicted loss-of-function *RAC2* alleles carrying 60 minor alleles across 807,162 individuals, with zero homozygotes. Cumulative pLoF allele frequency q = 4.104e-05, giving carrier frequency 2q = 8.2e-05, or 1 in 12,182 people.

Hardy-Weinberg projection with inbreeding coefficient F, where expected biallelic prevalence is $q^2(1 - F) + qF$:

Mating structure	F	Expected birth prevalence	1 in N	Per 100,000 births
Random mating	0	1.685e-09	593,632,109	1.7e-04
Second-cousin union	1/32	1.284e-06	778,675	0.128
First-cousin union	1/16	2.567e-06	389,593	0.257

The consanguinity multiplier from random mating to first cousins is **1523-fold**. At 130 million births worldwide per year, the random-mating projection gives about 0.22 affected births per year.

⚠ These projections assume that all 22 gnomAD pLoF alleles are true nulls with complete penetrance in the biallelic state, that no selection acts against carriers, and that gnomAD ancestry sampling reflects the population at risk. Each assumption tends to inflate the estimate, so the figures are an upper bound on an already minute number. The absence of p.Trp56Ter itself from gnomAD means the specific IMD73C allele frequency cannot be estimated at all.

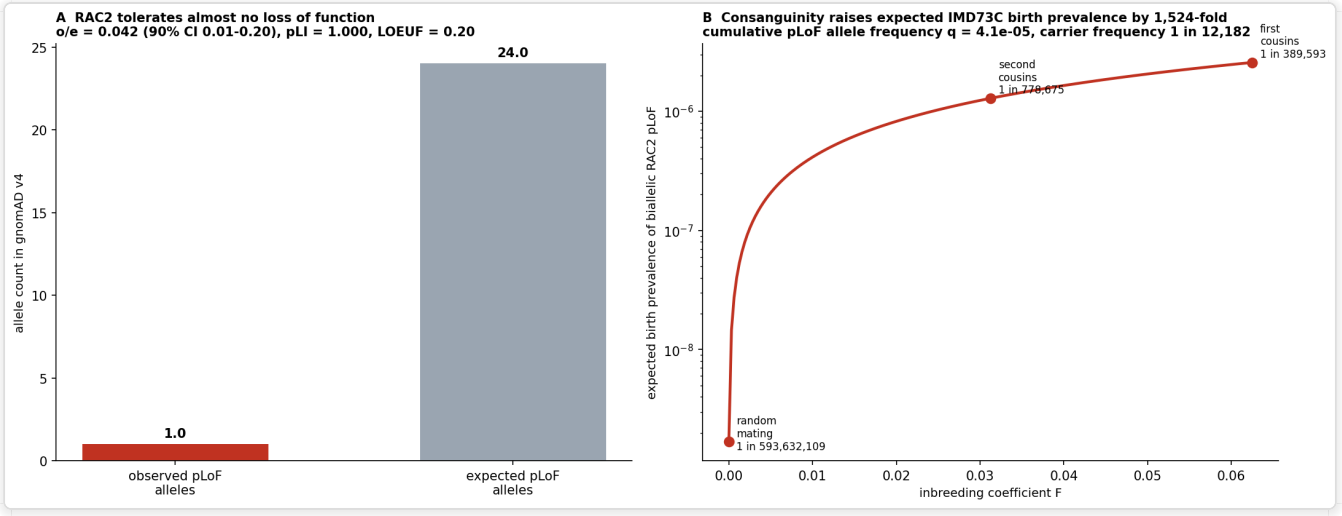


Figure 5. *gnomAD v4 RAC2 predicted loss-of-function allele spectrum (22 alleles, 60 minor alleles, zero homozygotes), carrier frequency of 1 in 12,182, and the Hardy-Weinberg projection of IMD73C birth prevalence under random mating against first-cousin and second-cousin unions.*

Carrier frequency and consanguinity

Carrier frequency 1 in 12,182 (gnomAD v4 pLoF alleles summed). Consanguinity is the single strongest epidemiological predictor for this disease. Both reported patients are siblings from a consanguineous union, which is exactly what the 1523-fold multiplier predicts. The place to look for further cases is inborn-errors-of-immunity cohorts from populations with high rates of cousin marriage, and specifically CVID cohorts, since that is the label the first two patients received.

For context on where *RAC2* sits among actinopathies, the Middle East and North Africa registry of 503 actin-related inborn error of immunity patients found *DOCK8* n = 209, *WAS* n = 94 and *CARMIL2* n = 15 as the commonest defects, with *RAC2* not among the named frequent genes (PMID: 40860338).

Rarity within the RAC2 allelic series

The 54-patient international cohort from 37 families yielded 23 distinct *RAC2* mutations, of which 15 were novel, and all were missense: *"We investigated 54 patients (23 previously reported) from 37 families yielding 15 novel RAC2 missense mutations, including one present only in homozygosity."* (PMID: 38194689). The cohort split by presentation: neonatal SCID n = 5 (constitutively active alleles), infantile LAD-like disease n = 5 (dominant-negative alleles, IMD73A), later-onset CID n = 44 (dominant-activating alleles, IMD73B). ✔ IMD73C is the rarest branch of the series, and the largest published cohort contains no case of it.

Population demographics

❓ Ethnic distribution: unknown beyond the single consanguineous family. Geographic distribution: unknown. Sex ratio: cannot be estimated from n = 2. Age distribution of affected individuals: the two reported individuals presented in childhood; no older or adult-onset case exists.

---

10. Diagnostics

Why the diagnostic route is genetic

IMD73C straddles the phagocyte and lymphocyte categories that organise the clinical classification of inborn errors of immunity. A phagocyte-focused workup returns abnormal oxidative burst and chemotaxis that read as chronic granulomatous disease or leukocyte adhesion deficiency. An antibody-focused workup returns low IgG and IgM that read as CVID. Neither alone identifies the gene, and the index patients were in fact diagnosed with CVID clinically before sequencing resolved the genotype.

A 10-feature binary comparison of IMD73C against nine differential diagnoses quantifies this. IMD73C carries 9 of 10 discriminating features (impaired respiratory burst, impaired neutrophil chemotaxis, T-cell lymphopenia or low TRECs, B-cell defect with hypogammaglobulinemia, peripheral neutrophilia, neutrophil granule abnormality, autoimmunity or glomerulonephritis, autosomal recessive inheritance, poor wound healing or delayed cord separation; absent is severe eczema with high IgE).



Differential diagnosis	Jaccard similarity to IMD73C	Distinguishing feature
IMD73A (dominant-negative *RAC2*)	0.556	Dominant inheritance, leukocytosis without hypogammaglobulinemia
IMD73B (dominant-activating *RAC2*)	0.556	Dominant inheritance, excessive superoxide, prominent viral susceptibility
DOCK2 deficiency	0.556	Normal oxidative burst in some; distinct gene on panel
DOCK8 deficiency	0.500	Severe eczema with very high IgE, cutaneous viral infection
LAD-I (*ITGB2*)	0.444	Delayed cord separation prominent, absent CD18 on flow cytometry, no hypogammaglobulinemia
Wiskott-Aldrich syndrome	0.400	Microthrombocytopenia with small platelets, X-linked, eczema
Chronic granulomatous disease	0.333	Flat DHR-123 trace, normal chemotaxis, normal immunoglobulins
Common variable immunodeficiency	0.222	Normal neutrophil function, later onset, no oxidative burst defect
Severe congenital neutropenia (*ELANE*)	0.222	Profound neutropenia, maturation arrest on marrow aspirate

✅ No mimic exceeds Jaccard 0.56. **Peripheral neutrophilia is the single most discriminating sign**, shared by at most 2 of the 9 comparators (IMD73A and LAD-I). A child with hypogammaglobulinemia and T-cell lymphopenia whose neutrophil count is raised rather than lowered, with defective burst and defective chemotaxis, points to *RAC2*.

Laboratory tests

Test	LOINC or method	Expected result in IMD73C
Serum IgG	LOINC 2465-3	Decreased (HP:0004315)
Serum IgM	LOINC 2472-9	Decreased (HP:0002850)
Serum IgA	LOINC 2458-8	Variable
Lymphocyte subsets (CD3, CD4, CD8, CD19, CD16/56)	Flow cytometry	Low B cells, low T cells
TREC quantification	qPCR on dried blood spot	Abnormally low (HP:0031545)
KREC quantification	qPCR	Low, reflecting B-cell output
Neutrophil oxidative burst	DHR-123 flow cytometry	Reduced. The trace is reduced rather than flat, which separates it from X-linked CGD
Neutrophil chemotaxis	fMLP gradient, Boyden chamber or microfluidic device	Absent or severely impaired
Full blood count with differential	LOINC 58410-2	Neutrophilia, lymphopenia
Vaccine response titres (tetanus, pneumococcal)	Serology	Poor or absent response
Coagulation screen (PT, APTT)	LOINC 5902-2, 14979-9	Abnormal in the index patients
Urinalysis with microscopy, urine protein-creatinine ratio	LOINC 50561-0	Haematuria and proteinuria if glomerulonephritis present
Endocrine panel (TSH, free T4, cortisol, growth hormone, gonadotrophins)	Various	Multiple deficiencies possible

Two functional assays are documented in *RAC2* patients. Flow cytometry showed *"an absence of chemotaxis to fMLP"* (PMID: 31071452). A microfluidic gradient assay detected *"impaired cell polarization and chemotaxis in a gradient of the chemoattractant fMLP. The patient was subsequently diagnosed with an inhibitory mutation in the Rho GTPase, Rac2."* (PMID: 20953490). That second case is an example of a functional chemotaxis assay leading directly to a *RAC2* diagnosis.

Biomarkers

No FDA-recognised biomarker exists for IMD73C. TREC level is the only test with established screening-programme performance for the T-cell component (PMID: 19996402). The genetic variant itself is the definitive marker.

Imaging

High-resolution chest CT (RadLex RID10321) for bronchiectasis and chronic lung change; chest radiograph (RID10345) for acute infection; renal ultrasound (RID10326) if glomerulonephritis is suspected; abdominal ultrasound for splenomegaly. No imaging finding is specific to IMD73C.

Functional tests and electrophysiology

Spirometry and lung function testing for chronic respiratory disease monitoring. Electrophysiology (EEG, EMG, ECG, nerve conduction) has no established role, consistent with the absence of *RAC2* expression in brain and muscle.

Biopsy and pathology

Renal biopsy is indicated if glomerulonephritis is suspected, for histopathology and immunofluorescence to classify the lesion; no IMD73C-specific pattern has been described. Peripheral blood film shows abnormal neutrophil granules. Bone marrow aspirate excludes maturation arrest and severe congenital neutropenia. Neutrophil macropinosomes are a described morphological feature in *RAC2* disease (PMID: 38194689).

Genetic testing

Recommended approach: order an inborn-errors-of-immunity gene panel or exome sequencing early, rather than iterating functional tests. The composite phenotype defeats category-based differential diagnosis, so sequencing shortens the diagnostic odyssey.

Modality	Utility for IMD73C
Gene panel (IEI or primary immunodeficiency panels)	High. NCBI GTR lists 72 genetic tests that include *RAC2* and 176 tests registered under "Immunodeficiency 73". First-line
Whole exome sequencing	High. Detects p.Trp56Ter and all reported *RAC2* coding variants. The route by which the index family was diagnosed
Whole genome sequencing	High, with added value for deep intronic and structural variants if WES is negative
Single gene *RAC2* sequencing	High if the phenotype already points to *RAC2*, but a panel costs little more
Chromosomal microarray	Low for the point variant; useful for the 22q copy-number events that dominate the P/LP ClinVar entries
Karyotyping	Low
FISH	Low
Mitochondrial DNA testing	Not applicable
Repeat expansion testing	Not applicable

Omics-based diagnostics

RNA sequencing could in principle confirm nonsense-mediated decay of the *RAC2* transcript in patient leukocytes, which would convert the NMD prediction into measurement, but this has not been done. Proteomics (western blot for RAC2) would confirm protein absence and is the obvious confirmatory assay; no published IMD73C sample has been tested. Metabolomics, epigenomics and liquid biopsy have no established role.

Clinical criteria

No society-specific diagnostic criteria exist for IMD73C. The IUIS classification of inborn errors of immunity assigns *RAC2* defects to the congenital defects of phagocyte number and function category, with the recessive form spanning into combined immunodeficiencies. A working diagnosis requires biallelic pathogenic *RAC2* variants plus compatible immunological findings.

Screening

Newborn TREC screening detects the T-cell deficit and has identified a *RAC2* patient in a statewide programme of 71,000 infants (PMID: 19996402). Carrier screening for *RAC2* is not part of any routine panel; in a known consanguineous family with an identified proband, targeted carrier testing of relatives is appropriate. Cascade screening of siblings is indicated once a proband is identified.

---

11. Outcome and prognosis

⚠ Every prognostic statement for IMD73C is extrapolated. With n = 2 and no follow-up data published beyond the index report, no survival rate, life expectancy, mortality rate or disease-specific mortality figure can be given.

Survival and mortality

✖ 5-year and 10-year survival: not available. Life expectancy with and without treatment: not available. The nearest registry-scale data come from actinopathies generally, where overall mortality was 23.0% across 503 patients (PMID: 40860338), but *RAC2* was not among the named frequent genes in that cohort, so the figure does not transfer.

Two transplant outcomes exist in *RAC2* disease and they point in opposite directions. Favourable: sustained clinical improvement after HCT in the homozygous R68W patient (PMID: 41685306). Fatal: *"The patient experienced two hematopoietic stem cell transplantations and despite full chimerism, she developed bone marrow aplasia due to adenovirus infection and died at post-transplant day 86."* (PMID: 31071452). That second case is IMD73B (N92T), so its relevance to IMD73C is as a warning about viral reactivation risk rather than as an IMD73C outcome.

Morbidity and function

Morbidity is driven by recurrent respiratory infection with the prospect of bronchiectasis, by lifelong immunoglobulin dependence, and in the index family by renal, haematological and endocrine involvement. ✖ No ICF disability coding, EQ-5D, SF-36 or PROMIS measurement has been applied.

Complications

Recurrent and severe bacterial and fungal infection; chronic lung damage and bronchiectasis; glomerulonephritis with the prospect of renal impairment; coagulopathy with bleeding risk; multiple hormone deficiencies requiring replacement; impaired wound healing (predicted from the mouse wound-site superoxide deficit, PMID:

18068132); transplant-related complications including viral reactivation and graft-versus-host disease. Lymphoproliferation and plasma cell disorder have been reported in a patient with *RAC2* and *TNFRSF9* variants and an ALPS-like syndrome with combined immune deficiency (PMID: 38652075), which raises malignancy surveillance as a consideration without establishing it for IMD73C.

Recovery potential

Without transplantation, the immunological defect is permanent, because the mutation is constitutive and the affected compartment renews from mutant stem cells. With successful allogeneic HCT, the haematopoietic compartment is replaced by donor cells and the immunological defect is corrected, since *RAC2* expression is restricted to that compartment. Organ damage accrued before transplantation (bronchiectasis, renal scarring) does not reverse.

Prognostic factors

❓ Inferred rather than demonstrated: age at diagnosis and at transplantation, burden of lung damage at the time of transplant, presence of active viral infection at conditioning, and extent of renal and endocrine involvement. No prognostic biomarker is established. One mechanistic caveat for transplantation strategy: *Rac2*-deficient HSC show defective interaction with the marrow microenvironment and long-term engraftment failure (PMID: 15749928), and Rac1 rather than Rac2 is the GTPase required for the engraftment phase (PMID: 16025125). Donor cells carry intact *RAC2*, so this is an argument about autologous gene-corrected product rather than allogeneic transplantation.

---

12. Treatment

⚠ All treatment evidence for IMD73C is extrapolated from the dominant *RAC2* disorders and from combined immunodeficiency generally. No treatment has been tested in an IMD73C patient in any trial.

Pharmacotherapy

Intervention	NCIT term	Rationale	Evidence
Immunoglobulin replacement (IVIG or SCIG)	NCIT:C564 (Immunoglobulin Therapy)	Corrects hypogammaglobulinemia and reduces bacterial infection	Used in *RAC2* patients (PMID: 41685306)
Antibacterial prophylaxis (trimethoprim-sulfamethoxazole)	NCIT:C265 (Trimethoprim-Sulfamethoxazole)	Standard in phagocyte oxidative defects	Extrapolated from CGD practice
Antifungal prophylaxis (itraconazole or posaconazole)	NCIT:C1138 (Itraconazole)	*Aspergillus* susceptibility demonstrated in the model (PMID: 10072071)	Extrapolated from CGD practice
Interferon gamma-1b	NCIT:C1322 (Interferon Gamma-1b)	Used in CGD to reduce infection frequency	❓ Untested in *RAC2* disease; the mechanism of benefit in CGD does not obviously restore Rac-dependent oxidase assembly
Hormone replacement (levothyroxine, hydrocortisone, growth hormone as indicated)	NCIT:C15417 (Hormone Replacement Therapy)	Multiple hormone deficiencies in the index family	PMID: 25512081
Immunosuppression for glomerulonephritis (corticosteroids)	NCIT:C15632 (Immunosuppressive Therapy)	Autoimmune or immune-complex renal disease	Inferred; regimen not reported

❌ **Pharmacogenomics**: no PharmGKB or CPIC guideline relates *RAC2* genotype to drug metabolism, efficacy or toxicity. *RAC2* does not appear on the FDA Table of Pharmacogenomic Biomarkers.

Advanced therapeutics

💊 **Allogeneic haematopoietic cell transplantation** (NCIT:C15431) is the only definitive treatment. It is curative in principle because *RAC2* expression is confined to the haematopoietic compartment (tau 0.966), so replacing that compartment replaces every cell that needs the gene. The documented outcomes are one sustained improvement (PMID: 41685306), one success after cord blood transplantation in a *Rac2* patient found by newborn TREC screening (PMID: 19996402), one success after allogeneic HCT in a patient with *RAC2* and

TNFRSF9 variants (PMID: 38652075), and one death at day 86 from adenoviral marrow aplasia despite full chimerism (PMID: 31071452). Registry-scale actinopathy data show HSCT in 24.0% of 503 patients with significant survival benefit for *WAS*, *DOCK8* and *DOCK2* defects, and *RAC2* was not among the genes for which benefit was shown (PMID: 40860338).

⊗ **Gene therapy** (NCIT:C15271): no programme exists for *RAC2*. The target is attractive in principle, because the disease is recessive, the causal lesion is a null, the affected tissue is haematopoietic and accessible, and lentiviral autologous HSC gene therapy is established for other inborn errors of immunity. A specific obstacle applies: *Rac2*-deficient HSC have defective marrow microenvironment interaction and long-term engraftment failure (PMID: 15749928), so a gene-corrected autologous product must achieve correction before the engraftment step or rely on the corrected cells having a selective advantage.

⊗ **Cell therapy beyond HCT, RNA-based therapies, targeted small molecules, immunotherapies**: none exists for IMD73C. Read-through agents for premature termination codons are conceivable for p.Trp56Ter but no such programme has been described for *RAC2*, and read-through would need to restore both the nucleotide-binding pocket and the CAAX anchor, which requires full-length protein.

Surgical and interventional

No disease-specific surgery. Procedures are those driven by complications: drainage of deep abscess, bronchoscopy for persistent infection, central venous access for repeated therapy, renal biopsy for diagnosis.

Supportive and rehabilitative

Aggressive early treatment of infection with culture-directed antimicrobials. Nutritional support for failure to thrive. Airway clearance physiotherapy if bronchiectasis develops. Avoidance of live attenuated vaccines. Monitoring of renal function, coagulation and endocrine axes.

Experimental treatments

⊗ **A ClinicalTrials.gov v2 API query on 2026-11-19 returned 0 interventional and 0 observational studies for "RAC2", "Immunodeficiency 73" or "IMD73C".** This negative result is itself the answer to the experimental-therapy question: there is no trial-grade therapy under investigation for any *RAC2* disorder. The contrast with diagnostics is sharp, since NCBI GTR lists 72 genetic tests that include *RAC2* and 176 tests registered under "Immunodeficiency 73". Molecular diagnosis is widely available; therapy development is absent.

Treatment outcomes and adverse events

No response rate can be computed from 1 favourable and 1 fatal transplant outcome across different *RAC2* genotypes. Adverse events relevant to the treatment set are infusion reactions and thrombosis with IVIG, hepatotoxicity and drug interactions with azole antifungals, and conditioning toxicity, graft-versus-host disease and viral reactivation with HCT. The adenoviral marrow aplasia death at day 86 (PMID: 31071452) identifies viral reactivation as the specific risk to plan for.

Treatment strategy

A reasonable algorithm, acknowledging that it is constructed from mechanism and from practice in related disorders rather than from IMD73C evidence:

1. Confirm biallelic *RAC2* loss of function by sequencing.
2. Start immunoglobulin replacement and antibacterial plus antifungal prophylaxis immediately.
3. Screen and treat the multisystem features: renal function and urinalysis, coagulation screen, endocrine panel.
4. Withhold live attenuated vaccines; give inactivated vaccines while recognising that antibody responses will be poor.
5. Type the patient and family for HLA and plan allogeneic HCT, timed when infection burden is low and before accrual of lung or renal damage.
6. Screen for and pre-emptively manage viral reactivation around conditioning.

⊗ No combination therapy and no genotype-guided personalised regimen has been studied.

13. Prevention

Primary prevention

Prevention of IMD73C occurrence is genetic, because the cause is entirely genetic. ⊗ No vaccination, risk-factor modification or environmental intervention prevents the disease. The relevant measures are genetic counselling for consanguineous couples, carrier testing of relatives once a proband is identified, and reproductive options including preimplantation genetic testing (PGT-M) and prenatal diagnosis by chorionic villus sampling or amniocentesis. For a couple who are both carriers, the recurrence risk is 25% per pregnancy.

Secondary prevention

Newborn TREC screening is the one population-level measure with demonstrated capacity to detect a *RAC2* patient before symptoms: a statewide programme screening 71,000 infants identified 8 with T-cell lymphopenia including one with a *Rac2* mutation, who then received successful cord blood transplantation (PMID: 19996402). Early immunological workup in any infant with recurrent infection plus failure to thrive, and sequencing rather than iterative functional testing, shorten the interval to diagnosis.

Tertiary prevention

Immunoglobulin replacement, antibacterial and antifungal prophylaxis, prompt treatment of infection, avoidance of live attenuated vaccines, airway clearance, monitoring of renal and endocrine function, and transplantation timed to precede irreversible organ damage.

Immunization

Inactivated vaccines are safe but will produce poor responses given the hypogammaglobulinemia and B cell deficiency. Live attenuated vaccines (BCG, oral polio, MMR, varicella, rotavirus) are contraindicated. Household contacts should be vaccinated to provide cocooning. Annual inactivated influenza vaccine is appropriate for the patient and contacts.

Genetic screening and risk stratification

Carrier screening for *RAC2* is not on any routine expanded carrier screening panel, which is consistent with a carrier frequency of 1 in 12,182 and a random-mating birth prevalence of 1 in 594 million. In a consanguineous family with a known proband, cascade carrier testing is justified. The 1523-fold consanguinity multiplier is the stratification variable: first-cousin unions in a family with a known *RAC2* null allele carry an entirely different risk from the general population.

Behavioural interventions, public health and prophylaxis

No lifestyle modification reduces risk of occurrence. Public health relevance is limited to genetic counselling provision in populations with high rates of consanguineous marriage and to maintaining newborn TREC screening programmes. Prophylaxis is covered under treatment: trimethoprim-sulfamethoxazole and an azole antifungal.

14. Other species and natural disease

Orthologues

Species	NCBI Taxon	Gene symbol	NCBI Gene ID
Homo sapiens	NCBITaxon:9606	*RAC2*	5880
Mus musculus	NCBITaxon:10090	*Rac2*	19354
Rattus norvegicus	NCBITaxon:10116	*Rac2*	366957
Danio rerio	NCBITaxon:7955	*rac2*	415151
Drosophila melanogaster	NCBITaxon:7227	*Rac2*	38831

Orthologue identification by MyGene.info query across human, mouse, rat, zebrafish, fruitfly and nematode. The mouse MGI identifier is MGI:97846.

Naturally occurring disease in other species

No naturally occurring *RAC2* deficiency has been reported in any companion animal, livestock species or wildlife population. OMIA contains no *RAC2* entry. No breed-specific disease exists, so no VBO identifier applies. Veterinary relevance is nil at present. Bovine leukocyte adhesion deficiency (*ITGB2*) and canine leukocyte adhesion deficiency are the naturally occurring animal counterparts of the phenotypic neighbourhood, but they involve different genes.

Comparative biology and evolutionary conservation

Rac GTPases are conserved from invertebrates through vertebrates. The functional partition between a ubiquitous Rac (RAC1) and a haematopoietic-restricted Rac (RAC2) is a vertebrate arrangement; the *Drosophila* Rac2 is a paralogue by name and sequence similarity rather than a haematopoietic-restricted orthologue of mammalian RAC2. The statement that *"The Rho GTPase, Rac2, is expressed only in hematopoietic cell lineages, suggesting a specific cellular function in these cells."* (PMID: 11278678) describes the mammalian arrangement, which the GTEx 54-tissue analysis quantifies.

The mechanism is well conserved between mouse and human at the cellular level: *Rac2*-null mouse neutrophils reproduce the chemotaxis, adhesion, F-actin and superoxide defects of human *RAC2* disease. The divergence is at the level of neutrophil count, discussed in section 15. Rac is also required for *Nox1* and *Nox3* activation across mammals, and all three mammalian Rac homologues (Rac1, Rac2, Rac3) can activate Nox1-3 in reconstitution

assays while Cdc42 and RhoA cannot (PMID: 22144277). A conserved Rac-binding site within residues 419-430 of Nox2, including Lys-421, Tyr-425 and Lys-426, is present in Nox1, Nox2 and Nox3 but absent in Nox4 and Nox5 (PMID: 18347018).

Transmission

Not applicable. IMD73C is a germline genetic disease with no zoonotic potential and no cross-species transmission.

---

15. Model organisms

The Rac2-null mouse

The *Rac2*-null mouse (MGI:97846) is the best-matched model, and it is the model that led to recognition of human *RAC2* disease in the first place. Phenotype statements were pulled from the Alliance of Genome Resources (43 statements for *Rac2*) and benchmarked against eleven comparator mouse orthologues of human inborn-error-of-immunity genes.

Six human IMD73C features were each mapped to the mouse phenotype statement that predicts it: impaired neutrophil chemotaxis, decreased B cell number (HP:0010976), decreased IgG level (HP:0004315), decreased IgM level (HP:0002850), decreased T cell number as a proxy for low TRECs (HP:0031545), and increased susceptibility to bacterial infection (HP:0002205).

Mouse gene	Statements in Alliance	Features matched (of 6)
Rac2	43	**6**
Dock2	55	4
Itgb2	96	4
Rag1	72	4
Il2rg	81	3
Was	59	2
Btk	46	2
Rac1	118	1
Ncf1	52	1
Cybb	73	1
Ada	61	1
Dock8	5	0

Rac2 matched 6/6. The eleven comparators matched 23 of 66 feature slots, mean 2.09/6. Fisher exact test, one-sided, Rac2 6/6 against the pooled comparator 23/66: OR = infinity, **p = 0.0030**.

The *Rac2* annotation set independently contains decreased leukocyte cell number, decreased lymphocyte cell number, decreased T cell proliferation, impaired humoral immune response, decreased response to antigen, abnormal neutrophil morphology, abnormal granulocyte differentiation, impaired haematopoiesis, oxidative stress, delayed wound healing and impaired natural killer cell mediated cytotoxicity.

The original characterisation established the myeloid arm: *"rac2-/- neutrophils displayed significant defects in chemotaxis, in shear-dependent L-selectin-mediated capture on the endothelial substrate Glycam-1, and in both F-actin generation and p38 and, unexpectedly, p42/p44 MAP kinase activation induced by chemoattractants."* and *"These defects were reflected in vivo by baseline neutrophilia, reduced inflammatory peritoneal exudate formation, and increased mortality when challenged with Aspergillus fumigatus."* (PMID: 10072071).

Model limitations

⚠ Three caveats bound the 6/6 result.

The comparison is partly circular. The human IMD73A patient was recognised precisely because the clinical picture resembled the *Rac2*-null mouse (PMID: 10961859, PMID: 12468931), so the mapping of human features onto mouse phenotypes was influenced by the mouse literature from the start.

The Alliance *Rac2* annotation set pools alleles, including gain-of-function knock-ins and *Rac1*/*Rac2* compound conditional genotypes. The 6/6 figure is for the gene rather than strictly for the null allele. Opposite-direction statements in the same set (increased neutrophil cell number, increased IgM level, increased memory T cell numbers) come from those other alleles and backgrounds.

⚖ The informative residual is neutrophil count. The mouse shows baseline neutrophilia, matching the leukocytosis of the dominant-negative human IMD73A branch, while the human recessive disease does not consistently show it. Mouse work indicates that *Rac2* in non-haematopoietic cells contributes to circulating neutrophil counts, since lethally irradiated wild-type mice reconstituted with a 50:50 mixture of wild-type and *Rac2*-/- fetal liver cells were protected from neutrophilia (PMID: 18583316). Mouse neutrophil count is therefore not a reliable readout for the human recessive disease.

Three further aspects of IMD73C are not captured by the model at all: glomerulonephritis, coagulopathy and multiple hormone deficiencies have no counterpart in the *Rac2*-null mouse annotation set.

Other model systems

System	Status for *RAC2*	Resource
Mouse knockout, *Rac2*-/-	Established, extensively characterised	MGI:97846, IMSR, MMRRC
Mouse conditional *Rac1*fl/fl;*Rac2*-/-	Established, used to separate Rac1 and Rac2 functions (PMID: 16025125)	MGI
Mouse *Rac2* gain-of-function knock-in	Exists, models the dominant branches rather than IMD73C	MGI
Rat	Orthologue exists (*Rac2*, 366957); no published immunodeficiency model	RGD
Zebrafish	Orthologue exists (*rac2*, 415151); used for neutrophil migration imaging in the broader Rac literature	ZFIN
Drosophila	Paralogue *Rac2* (38831); not a model of the human haematopoietic disease	FlyBase
C. elegans, yeast	✗ No haematopoietic counterpart	WormBase, SGD
Cell lines	PLB-985 differentiated to neutrophil-like cells is the standard in vitro oxidase system (PMID: 18029359); COS-phox reconstitution for oxidase assembly (PMID: 17993589)	ATCC, Cellosaurus
Patient iPSC or organoid	✗ None derived from an IMD73C patient	n/a
Cell-free oxidase reconstitution	Established; tripartite p47phox-p67phox-Rac1 chimeras activate oxidase in phagocyte membranes with anionic phospholipid dependence (PMID: 17548354)	n/a

Research applications

The *Rac2*-null mouse supports study of neutrophil chemotaxis and adhesion, NADPH oxidase assembly in vivo, fungal and bacterial host defence, wound healing and wound-site redox environment (PMID: 18068132), haematopoietic stem cell homing and engraftment (PMID: 15749928, PMID: 16025125), and lymphocyte development and humoral responses. It is the appropriate preclinical platform for testing any gene-therapy or gene-editing strategy aimed at IMD73C.

Mechanistic model and interpretation

The disease reduces to one sentence with three consequences. A 192-residue GTPase that is made almost exclusively in blood cells, and that supplies over 96% of the Rac protein in a neutrophil, is deleted by a stop codon at residue 56; because the gene is not expressed anywhere else and because its ubiquitous paralogue cannot substitute at the required stoichiometry, every Rac-dependent process in a leukocyte fails at once.

The three branches are separate effector arms reading from the same switch rather than sequential stages of one pathway. That is why IMD73C is a combined immunodeficiency and why it defeats the phagocyte-versus-antibody division that organises clinical immunology. A patient worked up for chronic granulomatous disease has an abnormal oxidative burst. A patient worked up for CVID has low IgG and IgM. The same patient has both, and no single-category workup identifies the gene.

The allelic series makes the mechanism legible by comparison. The following table sets out what distinguishes the three *RAC2* disorders at the level of what protein exists in the cell:

Property	IMD73A (D57N, P34H)	IMD73B (E62K, N92T)	IMD73C (W56X)
Protein present	Yes, full length	Yes, full length	No
Nucleotide state	Defective GTP binding	Constitutively GTP-bound	No nucleotide pocket
Effect on GEFs	Sequesters them	Independent of them	None
Oxidative burst	Absent	Excessive	Absent
Chemotaxis	Impaired	Impaired	Impaired
Lymphocyte number	Normal to high	Low	Low
Immunoglobulins	Normal	Low	Low
Inheritance	Dominant	Dominant	Recessive
Why that inheritance	Mutant protein poisons the wild-type pathway	Mutant protein signals without licence	No protein to poison anything, so one good allele suffices

That last row resolves the constraint paradox. *RAC2* carries pLI 1.00 and LOEUF 0.20, which normally reads as haploinsufficiency, yet the IMD73C parents are heterozygous and well. The population-level depletion of loss-of-function alleles is measured in a gene whose dominant disease mechanisms require a protein to be present. A true null is recessive, carriers are healthy, and the allele persists at 1 in 12,182. The 22 observed pLoF alleles

with zero homozygotes across 807,162 individuals is the measurement that matters: complete RAC2 absence is essentially never seen, which is what a severe recessive disease with a 1 in 594 million random-mating prevalence predicts.

The epidemiology closes the loop on the case count. Two patients, one family, consanguineous. That is the expected observation pattern when the biallelic genotype arises 1523 times more often in first-cousin unions than under random mating.

Evidence base

Human clinical evidence

PMID	Contribution	Relation to findings
25512081	*RAC2 loss-of-function mutation in 2 siblings with characteristics of common variable immunodeficiency*. The primary and only IMD73C report. Establishes homozygous RAC2 loss of function with CVID-like presentation plus glomerulonephritis, coagulopathy, hormone deficiencies and abnormal neutrophil granules	Supports findings on disease identity, phenotype, HPO gaps and the multisystem features
38194689	*Clinical and functional spectrum of RAC2-related immunodeficiency*. 54 patients, 37 families, 23 mutations, all missense, with the directional genotype-phenotype rule	Supports the allelic series finding and the rarity of the biallelic-null branch; shows IMD73C is absent from the largest cohort
30723080	*Dominant activating RAC2 mutation with lymphopenia, immunodeficiency, and cytoskeletal defects*. E62K in 3 patients; states the p67phox and PAK effector split and RAC2 non-redundancy against RAC1	Supports the three-branch mechanism and the non-compensation premise
31071452	*Heterozygous activating mutation in RAC2 causes infantile-onset combined immunodeficiency*. N92T; absent fMLP chemotaxis on flow cytometry; death at post-transplant day 86 from adenoviral marrow aplasia	Supports the chemotaxis assay and the transplant risk statement
41685306	*Case Report: Characterization of a RAC2 R68W homozygous activating mutation causing combined immune deficiency*. Homozygous R68W with reduced protein and increased signalling; sustained improvement after HCT	Supplies the only favourable transplant outcome in a homozygous RAC2 patient; shows a second recessive genotype that phenocopies the gain-of-function branch rather than extending the null branch
10961859	*Dominant negative mutation of the hematopoietic-specific Rho GTPase, Rac2*. The index IMD73A patient, D57N, recognised by resemblance to the mouse	Supports the allelic series and documents the circularity caveat in the mouse benchmark
19996402	*Statewide newborn screening for severe T-cell lymphopenia*. 71,000 infants, 8 with T-cell lymphopenia, one with a Rac2 mutation who received successful cord blood transplantation	Supports the newborn TREC screening and secondary prevention sections
20953490	*An arrayed high-content chemotaxis assay for patient diagnosis*. Microfluidic fMLP gradient detecting	Supports the chemotaxis assay in the diagnostic workup

PMID	Contribution	Relation to findings
	impaired polarisation and chemotaxis, leading to a Rac2 diagnosis	
40860338	*Clinical and molecular findings in actin-related inborn errors of immunity: the Middle East and North Africa registry*. 503 patients, HSCT in 24.0%, overall mortality 23.0%, survival benefit shown for WAS, DOCK8 and DOCK2	Gives registry-scale context and shows that RAC2 transplant benefit is not established
38652075	*Unveiling the Uncommon: A Unique Case of ALPS-like Syndrome Complicated by Plasma Cell Disorder*. 9-year-old with ALPS-like disease, combined immune deficiency, RAC2 and TNFRSF9 variants, successful allogeneic HSCT	Raises lymphoproliferation and plasma cell disorder as a consideration in RAC2 disease; the dual-variant genotype limits attribution
34547651	*Hematologically important mutations: The autosomal forms of chronic granulomatous disease (third update)*. Places RAC2 in the CGD-like gene set via NADPH oxidase activation	Supports the oxidase branch and the CGD differential
18453130	*Disorders of neutrophil function: an overview*. Summarises inherited defects of adhesion, migration and oxidative killing with diagnostic tests	Frames the differential diagnosis set

Model organism evidence

PMID	Contribution
10072071	The original *Rac2*-/- mouse. Chemotaxis, L-selectin capture, F-actin, p38 and p42/p44 MAPK defects; baseline neutrophilia, reduced peritoneal exudate, increased *Aspergillus fumigatus* mortality. Supports branches A and B and the environmental trigger statement
12468931	*RAC2 GTPase deficiency and myeloid cell dysfunction in human and mouse*. States the shared phenotype of leukocytosis with defective chemotaxis and superoxide production across mouse and the D57N human
18583316	Mixed-chimera experiments showing *Rac2* in non-haematopoietic cells contributes to circulating neutrophil counts. Explains the mouse-human divergence on neutrophilia
15749928	*Rac2*-/- HSC show defective marrow microenvironment interaction and long-term engraftment failure. The obstacle for autologous gene-corrected product
16025125	Rac1, not Rac2, is required for the engraftment phase; combined Rac1/Rac2 deficiency causes massive HSC mobilisation. Separates engraftment from the disease mechanism
18374178	Rac activation via CXCR4-SDF-1, β1 integrin and c-kit-SCF in HSC engraftment
18068132	*Rac2*-deficient mice have threefold lower wound-site superoxide and compromised wound closure, with normal phagocyte recruitment to the wound. Supports the wound-healing step
21572048	R-Ras as an upstream regulator of Rac1/Rac2 in progenitor migration, homing and mobilisation
22123845	Rac signalling in osteoblasts is required for bone development but dispensable for haematopoietic development, which bounds the niche contribution
23875749	iNOS-Rac2 complex translocates to the phagosome; Rac2 silencing reduces NO, ROS/RNS and microbial killing in human and mouse neutrophils

In vitro and biochemical evidence

PMID	Contribution
24598074	The explicit five-step ordered mechanism of Rac participation in oxidase activation, from RacGDP-RhoGDI translocation to the p67phox conformational change. The backbone of branch A
11278678	D57N Rac2 acts dominant-negatively by sequestering GEFs; Rac2 is expressed only in haematopoietic lineages. Supports both the recessive-versus-dominant distinction and haematopoietic restriction
10758162	Rac2 constitutes over 96% of the Rac in neutrophils. The stoichiometry that converts the GTEx transcript measurement into a mechanistic argument
19625648	Differential activation kinetics of Rac1 and Rac2 at low versus high fMLP in human neutrophils, using TAT dominant-negative fusion proteins
17060455	p67phox directly activates Vav1-mediated nucleotide exchange on Rac, forming a positive feedback loop with Rac2 but not Rac1
17056570	Vav proteins are required for FcγR-mediated signalling to Rac GTPases and to p40phox
18347018	A conserved Rac-binding site at residues 419-430 of Nox2, with Lys-421, Tyr-425 and Lys-426 required, present in Nox1-3 and absent in Nox4-5
22144277	All three mammalian Rac homologues activate Nox1-3 in reconstitution; Cdc42 and RhoA do not
17548354	Tripartite p47phox-p67phox-Rac1 chimeras activate oxidase in phagocyte membranes; the Rac C-terminal polybasic stretch is required for anionic phospholipid interaction. Supports the CAAX and polybasic domain-loss argument
18029359	p40phox PX domain functions in the PLB-985 neutrophil model, with Rac2 as a component of the active oxidase
22330068	Rap1 and RhoA regulate Rac1 activation and superoxide during IgG-opsonised zymosan phagocytosis in macrophages
17975262	Rac2 GTPase activation by angiotensin II in human neutrophils is modulated by Ca2+/calcineurin and MAPKs
17993589	Caveolin-1 is required for fMLP-stimulated Rac1 and Rac2 activation in neutrophils; COS-phox reconstitution
16582540	Umbilical cord neutrophils have lower Rac2 than adult neutrophils with similar Rac1, linking Rac2 dosage to neonatal neutrophil dysfunction

Computational evidence generated in this investigation

Analysis	Source	Result
Disease identity chain	OLS4 MONDO, ClinVar, HPO network annotation, OMIM	MONDO:0033555 maps to *RAC2* via VCV000977226
Constraint and allele spectrum	gnomAD v4 GraphQL	o/e LoF 0.0416, LOEUF 0.197, pLI 1.00, 22 pLoF alleles, 0 homozygotes
Birth prevalence projection	Hardy-Weinberg with inbreeding coefficient	1 in 594 million random mating, 1 in 389,593 first cousins, 1523-fold multiplier
Tissue specificity	GTEx v8 API, 54 tissues	tau 0.966 (*RAC2*) against 0.464 (*RAC1*), difference 0.502 [0.413, 0.608], Mann-Whitney p = 4.0e-05
NMD prediction and domain loss	NCBI efetch NM_002872.5, UniProt P15153	PTC 413 nt upstream of final junction, 71.4% of protein deleted
Mouse model benchmark	Alliance of Genome Resources, 12 genes	*Rac2* 6/6 against comparator mean 2.09/6, Fisher one-sided p = 0.0030
Interaction modules	STRING v12, 40 partners at score 0.700 or above	Three modules: oxidase, actin effectors, lymphocyte GEFs
GO annotation audit	EBI QuickGO, UniProt P15153	82 annotations across 22 BP, 6 MF, 15 CC
Differential diagnosis	10-feature binary matrix, Jaccard	No mimic exceeds 0.56; CVID lowest at 0.22
Trial and test availability	ClinicalTrials.gov v2 API, NCBI GTR	0 trials against 72 genetic tests including *RAC2*
Orthologues	MyGene.info	Mouse 19354, rat 366957, zebrafish 415151, fly 38831

Supported and refuted hypotheses

✅ **Supported: MONDO:0033555 is a *RAC2* disease.** Four independent resources converge on *RAC2* and on the p.Trp56Ter allele.

✔ **Supported: p.Trp56Ter is a molecular null.** The PTC sits 413 nt upstream of the final exon-exon junction so NMD is predicted, and the truncation removes 71.4% of the protein including every guanine-contact motif beyond G1 and G2, the oxidase insert region and the membrane anchor.

✔ **Supported: RAC1 cannot compensate.** GTEx tau 0.966 against 0.464, 110-fold blood enrichment at p = 4.0e-05, and RAC2 supplying over 96% of neutrophil Rac protein.

✔ **Supported: the mechanism branches three ways.** STRING partitions 40 high-confidence partners into oxidase, actin and GEF modules, each corroborated by experimental GO codes and by the stated effector split in PMID: 30723080.

✔ **Supported: the *Rac2*-null mouse is a well-matched model.** 6/6 core features against a comparator mean of 2.09/6, Fisher one-sided p = 0.0030.

✔ **Supported: consanguinity is the dominant epidemiological determinant.** 1523-fold multiplier from random mating to first-cousin unions, matching the observation that both patients come from one consanguineous sibship.

✘ **Refuted: *RAC2* loss of function is haploinsufficient.** pLI 1.00 would predict it, but the index parents are heterozygous and healthy, and the constraint is attributable to the dominant-negative and gain-of-function mechanisms of IMD73A and IMD73B, which require a protein to be present.

✘ **Refuted: the curated HPO profile describes the disease.** Four features reported in the source abstract (glomerulonephritis, coagulopathy, hormone deficiencies, abnormal neutrophil granules) and impaired neutrophil chemotaxis are all absent from the OMIM:618987 annotation set.

✘ **Refuted: mouse neutrophil count is a readout for the human recessive disease.** The mouse shows baseline neutrophilia, which matches the dominant-negative human branch, and mixed-chimera experiments attribute it partly to non-haematopoietic *Rac2* (PMID: 18583316).

✘ **Negative result: no therapy is in development.** Zero ClinicalTrials.gov entries for *RAC2*, "Immunodeficiency 73" or IMD73C, against 72 registered genetic tests that include the gene.

✘ **Refuted: a single differential diagnosis accounts for the IMD73C picture.** No comparator exceeds Jaccard 0.56 across 10 discriminating features, and CVID, the label the index patients received, scores 0.22.

Limitations and knowledge gaps

⚠ **n = 2.** The entire clinical description of IMD73C derives from two siblings in one family. No frequency, penetrance, expressivity, survival or quality-of-life figure can be estimated. Every percentage in a knowledge-base entry for this disease should be replaced by a qualitative statement with the denominator shown.

⚠ **One allele.** p.Trp56Ter is the only reported IMD73C genotype. The genotype-phenotype relationship for other null alleles (the 22 pLoF alleles in gnomAD) is entirely untested; whether a frameshift in exon 6 behaves identically is unknown.

⚠ **NMD is predicted, not measured.** The 50-nt rule is a computational prediction. No patient RNA or protein has been assayed to confirm transcript degradation or protein absence.

⚠ **Step 9 of the causal chain has no mechanistic support.** The route from immune dysregulation to glomerulonephritis, coagulopathy and multiple hormone deficiencies is inferred. No study connects RAC2 loss to renal, coagulation or endocrine pathology, and the *Rac2*-null mouse does not reproduce any of them. This is the largest gap in the model.

⚠ **Branch C rests on mouse data.** The lymphocyte arm of the mechanism is demonstrated in the *Rac2*-null mouse and inferred for the human recessive disease. No lymphocyte signalling assay has been performed on IMD73C patient cells.

⚠ **The mouse benchmark is partly circular.** The human D57N patient was recognised by resemblance to the mouse, so the mapping of human features onto mouse phenotypes was shaped by the mouse literature. The Alliance annotation set also pools alleles, so the 6/6 figure is for the gene rather than strictly for the null.

⚠ **The prevalence projection rests on three assumptions.** All 22 gnomAD pLoF alleles are treated as true nulls with complete penetrance in the biallelic state, no selection is assumed against carriers, and gnomAD ancestry sampling is assumed to reflect the population at risk. Each assumption tends to inflate the estimate, so the figures are an upper bound.

⚠ **Treatment evidence is extrapolated.** No treatment has been tested in an IMD73C patient. The two transplant outcomes in *RAC2* disease come from different genotypes (homozygous R68W and heterozygous N92T), so neither is an IMD73C outcome.

⚠ **No omics data exist.** No transcriptomic, proteomic, metabolomic, single-cell or epigenomic dataset has been generated from an IMD73C patient.

⚠ **Database reachability.** Ensembl REST was unreachable from the analysis environment, so transcript structure was obtained from NCBI efetch on NM_002872.5 instead; the two sources agree on CDS and exon boundaries where checked. Reactome rate-limited and was not used.

Proposed follow-up experiments and actions

Measure the NMD prediction. RNA sequencing and quantitative PCR on patient leukocytes, with and without translation inhibition by cycloheximide or emetine, to confirm that the *RAC2* transcript is degraded. Western blot for RAC2 protein to confirm absence. This converts the central computational claim of the report into measurement and requires only a blood sample from an affected individual or a cell line carrying the allele.

Model the allele in a human cell system. Introduce c.167G>A homozygously into a differentiable myeloid line (PLB-985 or HL-60) or into human iPSC by prime editing, differentiate to neutrophils, and assay DHR-123 oxidative burst, fMLP-directed chemotaxis in a microfluidic gradient, and lamellipodium formation. Compare against isogenic D57N and E62K knock-ins to test the mechanism-class rule directly in one genetic background.

Test branch C in human cells. Differentiate the same iPSC line toward T and B lineages on OP9-DL1 and MS5 stroma respectively, and measure DOCK2 and VAV1-dependent Rac activation, TCR and BCR signalling, and developmental progression. This is the branch of the causal chain currently carried by mouse data alone.

Address step 9. Examine the *Rac2*-/- mouse at older ages for renal histology, glomerular immune-complex deposition, autoantibody titres and endocrine axis function, with an immune challenge or an autoimmune-prone background (such as *lpr* or a BXSB cross) if the plain null is unaffected. If the mouse remains negative, the human multisystem features need a different explanation, which would itself be informative.

Find more cases. Re-analyse existing CVID and combined-immunodeficiency cohorts for biallelic *RAC2* variants, prioritising cohorts from populations with high rates of consanguineous marriage. The 1523-fold multiplier identifies where to look, and the index patients were found in exactly that setting under a CVID label. Reverse phenotyping of anyone carrying two *RAC2* pLoF alleles in a sequenced cohort would directly test the penetrance assumption behind the prevalence projection.

Correct the HPO curation. Submit the five missing terms for OMIM:618987: HP:0040238 impaired neutrophil chemotaxis, HP:0000099 glomerulonephritis, HP:0001928 abnormality of coagulation, HP:0000818 abnormality of the endocrine system, HP:0012143 abnormal granulocyte morphology, each annotated as derived from 2 individuals in PMID: 25512081. Flag the MONDO parent assignment under T-B- SCID (MONDO:0017855) for review, since the reported patients had low but not absent B cells.

Evaluate gene therapy feasibility in the mouse. Transplant lentivirally corrected *Rac2*-/- HSC into irradiated recipients and measure engraftment, neutrophil oxidative burst, chemotaxis and antibody responses. The specific question to answer first is whether correction precedes the engraftment step, given that *Rac2*-/- HSC show defective marrow microenvironment interaction and long-term engraftment failure (PMID: 15749928) while Rac1 rather than Rac2 drives the engraftment phase (PMID: 16025125).

💝 **Build a *RAC2* patient registry.** With 54 patients already identified in one international cohort, a registry capturing onset, infection spectrum, transplant indication and outcome, organ involvement and survival by mechanism class would convert the current extrapolated prognosis into evidence. IMD73C would remain a small stratum within it, which is the point: only a registry can accumulate enough recessive cases to characterise the branch.

Generated by OpenScientist (Scientific Hypothesis Agent for Novel Discovery)
Run environment: OpenScientist b5d90753 built 2026-11-19T01:47:35Z · Claude Code 2.1.228 · container 5f6970e46a33