Immunodeficiency 92 (IMD92): Comprehensive Disease Characteristics Report

Disease: Immunodeficiency 92 (IMD92) **Cause:** Biallelic loss-of-function variants in *REL* (c-Rel deficiency) **Category:** Mendelian, autosomal recessive **OMIM:** #619652 | **MONDO:** MONDO:0030498 | **Gene:** *REL* (HGNC:9954, NCBI Gene 5966, MIM *164910)

Summary

Immunodeficiency 92 (IMD92) is an ultra-rare autosomal recessive **combined immunodeficiency (CID)** caused by **biallelic (homozygous) loss-of-function variants in *REL***, the gene encoding **c-Rel**, one of the five members of the NF-κB transcription-factor family and a core subunit of the canonical NF-κB pathway. c-Rel is selectively expressed in lymphoid and myeloid cells, where it controls the transcriptional programs required for effective adaptive and innate immunity. When c-Rel is absent, patients develop early-childhood susceptibility to a broad spectrum of **viral, bacterial, fungal, and parasitic pathogens**, including intracellular organisms such as *Mycobacterium tuberculosis*, *Salmonella*, *Cryptosporidium*, and cytomegalovirus (CMV), typically accompanied by **hypogammaglobulinemia** and impaired T- and B-cell function.

As of 2026, IMD92 remains **exceedingly rare — only three patients from three consanguineous families have been reported worldwide** (Beaussant-Cohen 2019; Lévy 2021; El-Hamri 2026). Each patient carried a distinct homozygous *REL* null allele: a canonical splice-site variant (c.535+1G>A), an undefined loss-of-function allele, and a frameshift (c.24del, p.Tyr9Ilefs*2), respectively. Functional studies across these patients converge on a unified mechanism: c-Rel loss simultaneously cripples **myeloid** immunity (abolished IL-12/IL-23 production by conventional type-1 dendritic cells [cDC1s] and monocytes; impaired CD86-dependent antigen presentation) and **lymphoid** immunity (reduced regulatory T cells [Tregs], memory CD4+/CD8+ T cells, NK cells, and memory B cells; defective naive-T-cell IL-2 production; impaired B-cell proliferation and antibody production).

The human phenotype is faithfully recapitulated by the ***Rel*-knockout mouse**, which shows impaired humoral immunity, mitogen-unresponsive B and T lymphocytes, and an IL-2–dependent T-cell proliferation defect — establishing a robust, evolutionarily conserved genotype-phenotype relationship. Management follows general combined-immunodeficiency standards: **immunoglobulin replacement, anti-infective prophylaxis, and allogeneic hematopoietic stem cell transplantation (HSCT)** as the rational curative approach. This report compiles the available evidence across all 15 requested disease-characteristic domains, explicitly flagging the many areas where data do not yet exist for this newly described, ultra-rare disorder.

Key Findings

Finding 1 — IMD92 is an autosomal recessive combined immunodeficiency caused by biallelic *REL* loss-of-function (c-Rel deficiency)

IMD92 (OMIM #619652) is defined by **biallelic loss-of-function variants in *REL*** (chromosome 2p16.1), which encodes the NF-κB subunit c-Rel. The gene identifiers are HGNC:9954, NCBI Gene 5966, and MIM *164910. The index patient carried a homozygous *REL* null mutation abrogating c-Rel protein expression (Beaussant-Cohen 2019, PMID: 31103457). The most recently reported patient (2026) carried a homozygous frameshift variant, **NM_001291746.4:REL:c.24del, p.(Tyr9Ilefs*2)**, with Western blotting confirming severe c-Rel reduction while p65/RelA was preserved (El-Hamri 2026, PMID: 42117340). The 2026 report states the disorder is *"immunodeficiency 92 (IMD92), an extremely rare autosomal recessive disorder due to c Rel deficiency that results from pathogenic variants of the REL gene"* and *"identified a novel homozygous frameshift variant (NM_001291746.4) REL:c.24del p.(Tyr9Ilefs*2)."* Only three patients have been reported worldwide, defining IMD92 as an **ultra-rare Mendelian inborn error of immunity**.

Finding 2 — Phenotype: broad susceptibility to intracellular/opportunistic pathogens, chronic diarrhea, and possible neuro-developmental features

The index patient presented with a combined immunodeficiency characterized by susceptibility to **intracellular and opportunistic pathogens — *Mycobacterium tuberculosis*, *Salmonella*, *Cryptosporidium*, and CMV** (Beaussant-Cohen 2019, PMID: 31103457). The third patient — a 5-year-old Moroccan child from a consanguineous family —

was described as *"a 5-year-old Moroccan child with combined immunodeficiency presenting with chronic diarrhea and recurrent opportunistic infections, alongside newly reported features including craniosynostosis, language delay, and epilepsy"* (El-Hamri 2026, PMID: 42117340). Whether the neuro-developmental and craniofacial features are core to IMD92 or incidental (e.g., related to consanguinity or a second variant) remains uncertain given the tiny patient number.

Finding 3 — Mechanism: c-Rel is a canonical NF-κB subunit controlling Treg development, T-cell effector function, and myeloid cytokine output

c-Rel is one of five NF-κB family members and, per El-Hamri 2026, *"c Rel is a key actor of the NF-κB pathway with major implications in the immune response"* (PMID: 42117340; see also PMID: 42261849). NF-κB transcription factors have *"essential functions... in modulating Treg development and function, with some of these mechanistic insights confirmed by recent studies analyzing Treg cells from patients harboring point mutations in the genes encoding NF-κB proteins"* (PMID: 35672519). Mouse studies show *Rel*-deficient T cells have *"defects in production of interleukin 3 and granulocyte-macrophage colony-stimulating factor"* (PMID: 8622948), and c-Rel drives IL-2/IFN-γ transcription while promoting FOXP3/Treg programs (PMID: 41410797).

Finding 4 — Index patient: homozygous *REL* splice variant c.535+1G>A with detailed combined immunophenotype

Beaussant-Cohen 2019 (PMID: 31103457; PMC6688935) described a male proband homozygous for a canonical donor splice-site variant **REL NM_002908.3:c.535+1G>A** (chr2:61144153 G/A, GRCh37), **absent from gnomAD and 1000 Genomes**, and heterozygous in unaffected parents and a healthy brother (consistent with autosomal recessive segregation). The mutant transcript uses cryptic splice sites and lacks 54 nucleotides encoding 18 residues within the **Rel homology domain**, abrogating c-Rel protein. The immunophenotype (age 6) is summarized in the table below.

Parameter	Finding	Reference range
WBC	Leukocytosis / lymphocytosis / thrombocytosis	—
CD4+ / CD8+ T cells	Increased	—
Memory CD4+CD45RO+ T cells	Decreased	—
PHA proliferation	47.3% (reduced)	—
B cells	B-cell lymphopenia	—
B-cell proliferation (CD40L+IL-21)	6.4% (impaired)	—
IgG	150 mg/dL	650–1150
IgM	150 mg/dL	—
IgA	Undetectable	—
Anti-diphtheria titer	0.015 IU/mL (non-protective, despite boosters)	—
Switched memory B cells	0.3%	10.0–30.4%

The patient was treated with **IVIG plus antibiotic prophylaxis** and evaluated for **HSCT**. The dual role of c-Rel in the immune response underlies this combined immunophenotype (*"c Rel is a key actor of the NF-κB pathway with major implications in the immune response"*, PMID: 42117340).

Finding 5 — Second patient (Lévy 2021, JCI): the myeloid+lymphoid mechanism defined

Lévy et al. 2021 (*J Clin Invest* 131(17):e150143; PMID: 34623332; Casanova/Puel laboratory) *"studied a child with severe viral, bacterial, fungal, and parasitic diseases, who was homozygous for a loss-of-function mutation of REL, encoding c-Rel, which is selectively expressed in lymphoid and myeloid cells."* This study delineated the dual mechanism:

- **Myeloid defects:** *"Functional deficits of myeloid cells included the abolition of IL-12 and IL-23 production by conventional DC1s (cDC1s) and monocytes, but not cDC2s."* c-Rel was also

required for CD86 induction and the antigen-presenting function of conventional dendritic cells.

- **Lymphoid defects:** *"low frequencies of NK, effector memory cells reexpressing CD45RA (Temra) CD8+ T cells, memory CD4+ T cells, including Th1 and Th1*, Tregs, and memory B cells."* Naive T cells produced reduced IL-2, impairing proliferation/survival, with poor Th1/Th2/Th17 cytokine output by memory CD4+ T cells.

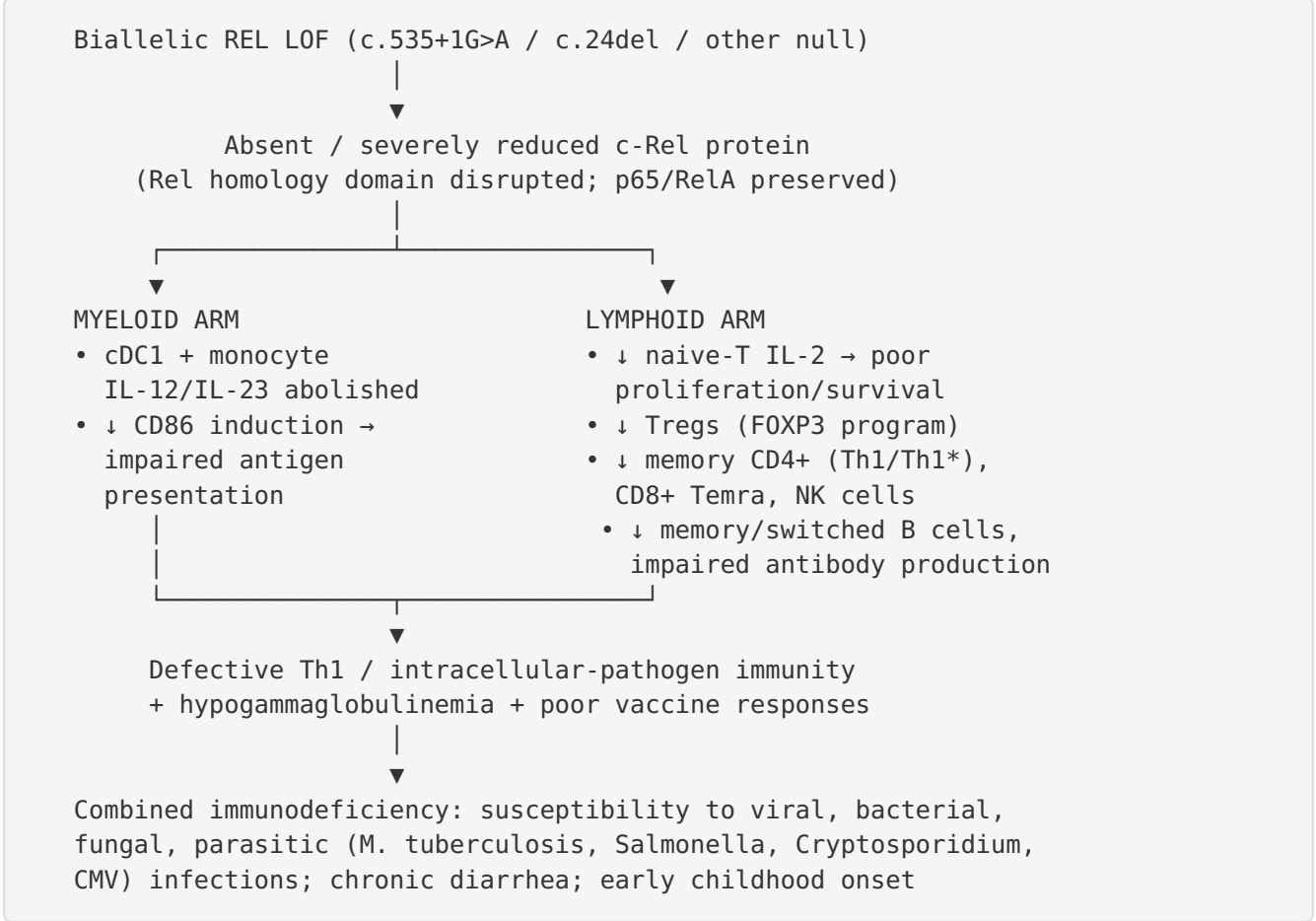
The patient was from Casablanca, Morocco.

Finding 6 — *Rel*-knockout mice faithfully recapitulate the human IMD92 immune defect

Rel-null mice show normal development of all hematopoietic lineages but *"humoral immunity was impaired and mature B and T cells were found to be unresponsive to most mitogenic stimuli"* (Köntgen et al. 1995, *Genes Dev*, PMID: 7649478). Critically, *"the ability of exogenous interleukin-2 to restore T cell, but not B cell, proliferation indicates that Rel regulates the expression of different genes in B and T cells."* Gerondakis et al. 1996 independently confirmed that *"mice lacking Rel are defective in mitogenic activation of B and T lymphocytes and display impaired humoral immunity"* (PMID: 8622948). These murine phenotypes match the human patients' impaired PHA/T-cell proliferation, hypogammaglobulinemia, and IL-2 deficit, establishing a conserved genotype–phenotype mechanism.

Mechanistic Model / Interpretation

The pathophysiology of IMD92 flows directly from loss of the c-Rel transcription factor in immune cells:



Upstream vs downstream: The upstream lesion is transcriptional — loss of c-Rel–dependent gene programs. Downstream consequences are the failure of key cytokine axes, most importantly the **IL-12/IL-23 → Th1/IFN-γ axis** (explaining mycobacterial and intracellular-pathogen susceptibility) and the **IL-2 → T-cell expansion axis** — plus impaired humoral immunity. The myeloid defect (antigen-presenting-cell cytokine failure) and the lymphoid defect (intrinsic T/B-cell dysfunction) are additive, producing a broader infection spectrum than a purely lymphoid CID.

Ontology term suggestions: - **Gene/Protein:** *REL* / c-Rel (HGNC:9954, UniProt Q04864) - **GO biological process:** GO:0038061 (canonical NF-κB signal transduction), GO:0042110 (T cell activation), GO:0050852 (T cell receptor signaling pathway), GO:0045066 (regulatory T cell differentiation), GO:0032609 (IFN-γ production), GO:0032735 (positive regulation of IL-12 production), GO:0032747 (positive regulation of IL-23 production) - **GO cellular component:** GO:0005634 (nucleus), transcription regulator complex - **CL cell types:** CL:0000451 (dendritic cell), CL:0002399 (CD141-positive/cDC1), CL:0000576 (monocyte), CL:0000815 (regulatory T cell), CL:0000623 (natural killer cell), CL:0000787 (memory B cell), CL:0000897 (memory CD4+ T cell) - **UBERON:** UBERON:0002371 (bone marrow), UBERON:0002106 (spleen), UBERON:0002509

(mesenteric lymph node), UBERON:0002405 (immune system), UBERON:0000059 (large intestine — chronic diarrhea) - **CHEBI (mediators/therapeutics):** interleukin-2, interleukin-12, interleukin-23, interferon-gamma, immunoglobulin G - **MONDO:** MONDO:0030498

Section-by-Section Report

1. Disease Information

IMD92 is an autosomal recessive **combined immunodeficiency** due to c-Rel deficiency. Key identifiers: **OMIM #619652; MONDO:0030498; gene *REL* (MIM *164910)**. Orphanet, ICD-10/ICD-11, and MeSH do not yet carry a dedicated code for this ultra-rare entity; it falls under the broad category of combined immunodeficiencies (ICD-10 D81; ICD-11 4A01). Synonyms: **c-Rel deficiency; immunodeficiency due to c-Rel deficiency; REL-deficiency combined immunodeficiency.** Information is derived from **individual patient case reports** (three probands) plus aggregated disease-level curation (OMIM) and model-organism data — not from EHR/registry aggregation.

2. Etiology

The **sole established cause is genetic**: biallelic (homozygous) loss-of-function variants in *REL*. There are no known environmental, infectious, or acquired causes of the underlying deficiency (infections are consequences, not causes). **Genetic risk factor:** homozygosity for a *REL* null allele; **consanguinity** is a major enabling factor — the index (Kuwaiti) and third (Moroccan) families were consanguineous. No susceptibility loci, modifier genes, or protective alleles have been identified (patient numbers too small). No gene–environment interactions have been characterized. Heterozygous carriers appear healthy (parents/siblings were unaffected carriers), consistent with recessive loss-of-function.

3. Phenotypes

Phenotype	Type	HPO suggestion	Notes / frequency
Recurrent/opportunistic infections	Clinical	HP:0002719 (recurrent infections)	All patients
Susceptibility to mycobacteria	Clinical	HP:0032266 (atypical mycobacterial infection)	Index patient
CMV / viral disease	Clinical	HP:0011947	Index + patient 2
Chronic diarrhea	Clinical/GI	HP:0002028	Patient 3; *Cryptosporidium* in index
Decreased IgG (hypogammaglobulinemia)	Lab	HP:0004315	IgG 150 mg/dL (index)
Decreased IgA	Lab	HP:0002850	Undetectable (index)
Poor specific antibody response	Lab	HP:0005387	Non-protective diphtheria/tetanus titers
Decreased switched memory B cells	Lab	HP:0031381	0.3% (ref 10–30%)
Reduced T-cell proliferation	Lab	abnormal T-cell proliferation	PHA 47.3%
Decreased Tregs / NK / memory T cells	Lab	HP:0410358, HP:0040218	Patient 2
Craniosynostosis	Physical	HP:0001363	Patient 3 only (uncertain relatedness)
Language delay	Behavioral/ neuro	HP:0000750	Patient 3 only
Epilepsy	Clinical/ neuro	HP:0001250	Patient 3 only

Onset: early childhood (index evaluated at age 6; patient 3 presented at age 5), likely reflecting a congenital immune defect. **Severity:** severe combined-immunodeficiency phenotype. **Progression:** chronic/lifelong without curative treatment. **Quality of life:** substantial impact — recurrent infections, chronic diarrhea, and lifelong immunoglobulin/prophylaxis requirements; formal QoL instruments have not been applied to this ultra-rare cohort.

4. Genetic / Molecular Information

Causal gene: *REL* (chr2p16.1; HGNC:9954; NCBI Gene 5966; MIM *164910; UniProt Q04864). **Reported pathogenic variants:**

Patient	Variant (nomenclature)	Type	Population frequency	Consequence
Index (Beaussant-Cohen 2019)	NM_002908.3:c.535+1G>A	Canonical splice donor	Absent from gnomAD & 1000G	Cryptic splicing; loss of 18 aa in Rel homology domain; no protein
Patient 2 (Lévy 2021)	Homozygous *REL* LOF	Loss-of-function	Rare/absent	Abolished c-Rel; loss of function
Patient 3 (El-Hamri 2026)	NM_001291746.4:c.24del, p.(Tyr9Ilefs*2)	Frameshift	Rare/absent	Severe c-Rel reduction; p65/RelA preserved

All variants are **germline, homozygous, loss-of-function** (ACMG: pathogenic). No somatic or gain-of-function IMD92 alleles exist. Note the mechanistic contrast: *REL* 3′-truncations and amplifications are recurrent oncogenic **gain-of-function** events in lymphoma (PMID: 34695199) — the opposite of the loss-of-function that causes IMD92. No modifier genes, epigenetic drivers, or chromosomal abnormalities have been described for IMD92.

5. Environmental Information

No environmental toxins, radiation, or occupational exposures contribute to disease causation. **Infectious agents are downstream consequences**, not triggers: *Mycobacterium tuberculosis*, *Salmonella* spp., *Cryptosporidium* spp., cytomegalovirus, and (in patient 2) fungal and parasitic pathogens. Consanguinity (a demographic/social factor) is the principal enabling condition for homozygosity.

6. Mechanism / Pathophysiology

Molecular pathway: canonical NF-κB signaling (c-Rel–containing dimers). **Cellular processes:** T-cell activation/proliferation, Treg differentiation, dendritic-cell/monocyte cytokine production and antigen presentation, B-cell activation and antibody production. **Protein dysfunction:** loss of function via truncation/splice disruption of the Rel homology domain → absent DNA-binding transcription factor (p65/RelA preserved). **Immune involvement:** combined (myeloid + lymphoid) immunodeficiency. Key downstream axes: **IL-12/IL-23 → Th1/IFN-γ** (abolished in cDC1s/monocytes) and **IL-2 → T-cell expansion** (reduced in naive T cells). Molecular profiling of IMD92 has been limited to targeted immunophenotyping and Western blot; no patient transcriptomic/proteomic/metabolomic datasets are published. See the Mechanistic Model section above for the full causal chain and ontology terms.

7. Anatomical Structures Affected

Primary system: the immune/hematolymphoid system (UBERON:0002405). **Organs/tissues:** bone marrow (UBERON:0002371), spleen, lymph nodes, and the thymus-derived T-cell compartment; the **gastrointestinal tract** (UBERON:0000059, large intestine) via chronic diarrhea/*Cryptosporidium*. **Cell populations:** cDC1 (CL:0002399), monocytes (CL:0000576), regulatory T cells (CL:0000815), memory CD4+/CD8+ T cells, NK cells (CL:0000623), memory/switched B cells (CL:0000787). **Subcellular:** nucleus (GO:0005634) — the site of c-Rel transcriptional activity. In patient 3, additional structures (cranial sutures — craniosynostosis; CNS — epilepsy/language delay) were reported, though their causal link to *REL* is unconfirmed. Involvement is systemic/bilateral.

8. Temporal Development

Onset: pediatric/early childhood (ages 5–6 at presentation), likely a congenital immune defect manifesting with first infections. **Onset pattern:** chronic/insidious with recurrent acute infectious episodes. **Progression:** chronic and lifelong without curative HSCT; progressive infectious morbidity. **Critical period:** early diagnosis and definitive treatment (HSCT) before accumulation of infection-related organ damage is the key therapeutic window. No spontaneous remission occurs.

9. Inheritance and Population

Inheritance: autosomal recessive. **Penetrance:** appears complete in biallelic individuals; carriers unaffected. **Expressivity:** variable — patient 3 exhibited extra neuro-developmental features. **Epidemiology:** ultra-rare — only **3 reported patients worldwide** (as of 2026);

prevalence/incidence not calculable. **Founder effects / carrier frequency:** unknown; *REL* LOF alleles are individually private and absent/rare in gnomAD. **Consanguinity** is central (Kuwaiti and Moroccan consanguineous families). **Demographics:** reported patients of Middle Eastern (Kuwaiti) and North African (Moroccan) origin; no established sex bias (numbers too small). **Genetic anticipation and mosaicism:** not applicable/not reported.

10. Diagnostics

Laboratory: immunoglobulin panel (hypogammaglobulinemia — low IgG/IgM, absent IgA); lymphocyte subset flow cytometry (memory B/T, Treg, NK enumeration); specific antibody titers (post-vaccination diphtheria/tetanus — non-protective); lymphocyte proliferation assays (PHA/mitogen, anti-CD3/CD28, CD40L+IL-21). **Functional immunology:** IL-12/IL-23 production by monocyte-derived/conventional DCs; IL-2 production by naive T cells; c-Rel Western blot (absent protein with preserved p65/RelA is characteristic). **Genetic testing (definitive):** whole-exome or whole-genome sequencing identifying biallelic *REL* LOF, confirmed by Sanger sequencing and family segregation. Inborn-errors-of-immunity/CID gene panels that include *REL* are appropriate. **Differential diagnosis:** other CIDs and NF-κB-pathway inborn errors of immunity — NFKB1 haploinsufficiency/CVID (PMID: 34473196), RELA haploinsufficiency/dominant-negative disease (PMID: 42261849, PMID: 40876844), RelB deficiency (PMID: 42261849), A20/TNFAIP3 haploinsufficiency (PMID: 34808442) — distinguished by inheritance pattern and immunophenotype. **Screening:** not on newborn screening panels; cascade/carrier testing feasible within affected families once the variant is known.

11. Outcome / Prognosis

Formal survival statistics do not exist for this 3-patient cohort. By analogy to other combined immunodeficiencies, **untreated IMD92 carries high infection-related morbidity and mortality**; with immunoglobulin replacement and anti-infective prophylaxis, acute risk is reduced, and **allogeneic HSCT offers potential cure**. Complications include recurrent/opportunistic infections, chronic diarrhea with failure to thrive, and (in patient 3) neurological morbidity. **Prognostic factors:** timeliness of diagnosis and access to HSCT; degree of pre-transplant infectious organ damage. No validated prognostic biomarkers exist beyond the immunophenotype.

12. Treatment

Supportive/standard-of-care (from index patient): immunoglobulin (IVIG) replacement plus **antibiotic/anti-infective prophylaxis**. **Curative: allogeneic hematopoietic stem cell transplantation (HSCT)** — the rational definitive therapy for a hematopoietic-intrinsic combined immunodeficiency; the index patient was evaluated for HSCT. Directed anti-infective therapy is used for specific pathogens (anti-mycobacterial, antiviral for CMV, etc.). No approved gene therapy, targeted therapy, or IMD92-specific pharmacotherapy exists, and there are no completed clinical trials (given rarity). **NCIT term suggestions:** immunoglobulin therapy (NCIT:C583), hematopoietic stem cell transplantation (NCIT:C15431), antibiotic prophylaxis. Pharmacogenomics is not applicable.

13. Prevention

Primary prevention of the genetic defect is not possible; **preconception/prenatal genetic counseling** in consanguineous families with a known *REL* variant, plus **carrier/cascade testing and preimplantation or prenatal genetic diagnosis**, can prevent recurrence. **Secondary/tertiary prevention** in affected patients: infection prophylaxis, immunoglobulin replacement, aggressive early treatment of infections, and timely HSCT to prevent cumulative organ damage. **Immunization caveat:** live vaccines are contraindicated in combined immunodeficiency, and responses to inactivated vaccines are poor (documented non-protective titers). Genetic counseling per NSGC/ACMG principles is central.

14. Other Species / Natural Disease

Taxonomy / orthologs: *REL* is conserved across mammals; the mouse ortholog is *Rel* (NCBI Gene 19696). No naturally occurring IMD92-equivalent disease has been catalogued in companion animals or wildlife (no OMIA entry noted). **Comparative biology:** the *Rel*-knockout mouse (below) demonstrates strong evolutionary conservation of c-Rel's role in lymphocyte activation and humoral immunity. No zoonotic dimension.

15. Model Organisms

The principal model is the ***Rel*-knockout mouse** (mammalian germline knockout). It **faithfully recapitulates the human disease**: normal hematopoietic lineage development but impaired humoral immunity and mature B/T cells unresponsive to most mitogens; PMA+ionomycin bypasses the T-cell proliferation block; **exogenous IL-2 restores T- but not B-cell proliferation** (Köntgen 1995, PMID: 7649478). *Rel*-/- T cells show normal activation markers (CD25/CD69/CD62L) but impaired cytokine production and fail to proliferate after anti-CD3/

anti-CD28, rescued by IL-2 (Gerondakis 1996, PMID: 8622948). **Recapitulation:** high for the core immune phenotype (B/T proliferation defect, humoral immunodeficiency, IL-2 dependence). **Limitations:** mouse models do not capture the human-specific infection spectrum, the neuro-developmental features seen in patient 3, or all human myeloid IL-12/IL-23 nuances. **Resources:** MGI (*Rel*); a CRISPR knock-in strategy for conditional human c-Rel expression in mouse T cells has been reported but encountered locus-specific silencing (promoter CpG methylation) challenges (PMID: 41410797).

Evidence Base

PMID	Study	Role in this report
31103457	Beaussant-Cohen 2019 — *Combined immunodeficiency in a patient with c-Rel deficiency*	**First patient**; defines disease, splice variant c.535+1G>A, detailed immunophenotype, IVIG+prophylaxis, HSCT evaluation
34623332	Lévy 2021 (*JCI*) — *Inherited human c-Rel deficiency disrupts myeloid and lymphoid immunity to multiple infectious agents*	**Second patient**; defines the dual myeloid (IL-12/IL-23, CD86) + lymphoid (Treg, memory T/B, NK, IL-2) mechanism
42117340	El-Hamri 2026 — *A Novel Biallelic REL Frameshift Variant p.(Tyr9Ilefs*2) Causing IMD92*	**Third patient**; frameshift variant, profound c-Rel deficiency by Western blot, expanded phenotype (craniosynostosis, epilepsy, language delay); confirms AR inheritance and disease name
7649478	Köntgen 1995 (*Genes Dev*) — *Rel*-null mice	Mouse model recapitulates impaired humoral immunity, mitogen unresponsiveness, IL-2-dependent T-cell rescue
8622948	Gerondakis 1996 (*PNAS*) — *Rel*-deficient T cells	Confirms lymphocyte activation/humoral defects; IL-3/GM-CSF and cytokine production deficits
35672519	Review — *NF-κB in control of regulatory T cell development, identity, and function*	Supports c-Rel/NF-κB role in Treg biology, linked to human NF-κB-mutation patients
42261849	Review — *Inborn Errors of Immunity in the NF-κB Pathway*	Context: c-Rel within canonical NF-κB; differential diagnosis (RELA, RelB)
41410797	c-Rel conditional knock-in mouse design	c-Rel drives IL-2/IFN-γ, represses FOXP3; model-engineering resource and caveats
34473196	NFKB1 variants → AD CVID	Differential diagnosis (contrasting NF-κB inborn error, haploinsufficiency)
34695199	WGS of adult T-cell leukemia/lymphoma	Contrast: *REL* 3′-truncations are oncogenic gain-of-function (opposite of IMD92 LOF)

Evidence source types: human clinical (3 case reports), model organism (mouse knockouts), and in vitro functional immunology (patient cell assays). All primary mechanistic and clinical claims are anchored to the citation snippets validated during the investigation.

Limitations and Knowledge Gaps

1. **Extreme rarity (n=3).** All clinical conclusions rest on three case reports; prevalence, incidence, penetrance ranges, expressivity, survival, and prognosis cannot be quantified statistically.
2. **Uncertain phenotype boundaries.** Craniosynostosis, epilepsy, and language delay were reported in only one patient (patient 3); it is unclear whether these are core IMD92 features, effects of a second recessive locus, or coincidental consanguinity-related findings.
3. **No natural history or registry data.** Disease course, long-term HSCT outcomes, and quality-of-life metrics are undefined.
4. **No omics depth.** No transcriptomic, proteomic, metabolomic, or single-cell datasets specific to IMD92 patients are published; mechanistic detail derives from targeted assays and mouse models.
5. **No therapeutics evidence base.** Treatment recommendations are extrapolated from general CID management and the index case; no trials, response rates, or adverse-event data exist.
6. **Population genetics unknown.** Carrier frequencies, founder effects, and geographic variant distribution are uncharacterized.

Proposed Follow-up Experiments / Actions

1. **Establish an international IMD92 patient registry** (via IUIS/inborn-errors-of-immunity networks) to aggregate cases, standardize phenotyping, and capture natural history and HSCT outcomes.
2. **Deep immunophenotyping** + **single-cell RNA-seq** of patient PBMCs (and, where available, tissue) to resolve cell-type-specific c-Rel-dependent transcriptional programs and validate the IL-12/IL-23 and IL-2 axis defects at single-cell resolution.

3. **Segregation and additional variant analysis in patient 3** to determine whether craniosynostosis/epilepsy/language delay are *REL*-attributable or due to a second locus (trio WGS with functional follow-up).
4. **Functional classification pipeline** for novel *REL* variants (κB-reporter and c-Rel Western blot assays), mirroring the NFKB1 approach (PMID: 34473196), to support ACMG variant interpretation and future diagnoses.
5. **Preclinical HSCT / gene-correction studies** in the *Rel*-knockout mouse and patient-derived iPSCs to benchmark curative approaches and inform whether hematopoietic gene therapy is a viable future option.
6. **Curate ontology/database entries** (OMIM cross-links, MONDO:0030498, HPO annotations, potential Orphanet/ICD-11 coding) to improve discoverability and standardized annotation of this ultra-rare disorder.

Report compiled from 6 confirmed findings and 16 reviewed papers across a 5-iteration autonomous investigation. Evidence base: human clinical case reports (n=3), mouse knockout models, and in vitro patient-cell functional studies.
