

Autoimmune Disease, Multisystem, Infantile-Onset, 2 (ADMIO2) — Comprehensive Disease Report

Disease: Autoimmune Disease, Multisystem, Infantile-Onset, 2 (ADMIO2) **MONDO ID:** MONDO:0014861 · **OMIM:** 617006 · **DOID:** 0061161 · **Category:** Mendelian (autosomal recessive inborn error of immunity) **Causal gene:** *ZAP70* (HGNC:12858, NCBI Gene 7535, UniProt P43403, locus 2q11.2)

Summary

Autoimmune disease, multisystem, infantile-onset, 2 (ADMIO2; MONDO:0014861 / OMIM 617006) is an ultra-rare, autosomal-recessive inborn error of immunity defined molecularly by **biallelic missense mutations in *ZAP70***, the Syk-family tyrosine kinase that is the proximal signaling node of the T-cell antigen receptor (TCR). The disease was delineated in a single sibling pair (a brother and sister) who were compound heterozygous for two private *ZAP70* alleles: a **hypomorphic allele, p.Arg192Trp (R192W)**, in the C-terminal SH2 domain that reduces binding to the phosphorylated ζ -chain, and an **activating allele, p.Arg360Pro (R360P)**, in the N-lobe of the catalytic domain that disrupts kinase autoinhibition to produce a weakly hyperactive enzyme ([PMID: 26783323](#)). This particular allelic combination distinguishes ADMIO2 from the more common classic *ZAP70*-deficiency combined immunodeficiency (CID; OMIM 269840), which is caused by biallelic loss-of-function alleles.

The defining pathophysiologic concept is that **altered TCR signal strength** — not simple loss of signaling — breaks T-cell tolerance. Attenuated/altered *ZAP70* kinase activity raises the thresholds of thymic (central) selection so that self-reactive thymocytes that should be negatively selected instead escape deletion and are positively selected, while the activating allele raises the sensitivity of mature peripheral T cells to weak self-ligands. The clinical result is severe, early-onset (first year of life) multiorgan autoimmunity — uncontrollable bullous pemphigoid, colitis, nephrotic syndrome with minimal-change glomerulonephritis, and a

factor VIII autoantibody causing acquired hemophilia — superimposed on a partial combined immunodeficiency with CD8 lymphopenia. Both affected children required and were cured by **allogeneic hematopoietic stem cell transplantation (HSCT)**.

This report synthesizes the molecular genetics, mechanism, phenotype, epidemiology, diagnostics, prognosis, treatment, and model-organism evidence for ADMIO2. Because ADMIO2 *sensu stricto* is known from a single family, much supporting mechanistic and clinical detail is extrapolated from (a) functional studies of the specific R360P and R192W alleles, (b) the broader literature on biallelic *ZAP70* deficiency (~49 reported patients), and (c) mouse models — the SKG hypomorphic mutant (Zap70 W163C) and an R360P knock-in — that respectively model the two human alleles. Importantly, ADMIO2 must be distinguished from the clinically similar but mechanistically unrelated **STAT3 gain-of-function syndrome (ADMIO1; OMIM 615952)**, which was also surveyed during this investigation.

1. Disease Information

Overview. ADMIO2 is a monogenic (Mendelian) disorder of immune dysregulation presenting in infancy with multisystem autoimmunity. Mechanistically it is an inborn error of TCR signaling: biallelic *ZAP70* variants alter the quality and strength of TCR signal transduction, breaking immune tolerance while simultaneously impairing protective T-cell immunity.

Key identifiers.

Resource	Identifier
MONDO	MONDO:0014861
OMIM	617006
DOID (Disease Ontology)	DOID:0061161
MedGen	C4310768 / CN934735
UMLS	C4310768
Gene	<i>ZAP70</i> — HGNC:12858, NCBI Gene 7535, UniProt P43403, Ensembl ENSG00000115085, locus 2q11.2

These cross-references were confirmed via OLS4/MONDO (MONDO:0014861 *equivalentTo* OMIM:617006).

Synonyms / alternative names. "ADMIO2"; the disease is best referred to by its OMIM title "Autoimmune disease, multisystem, infantile-onset, 2." The underlying gene-level entity is "ZAP70-related combined immunodeficiency / immune dysregulation." ADMIO1 (OMIM 615952) is the distinct STAT3-GOF syndrome.

Information source. Disease-level knowledge derives from aggregated resources (OMIM, MONDO, HPO) that are themselves built on a **single primary clinical report of two patients** (PMID: 26783323). This is a disease-level (literature-aggregated) rather than EHR/individual-patient derived entry, and the small n (2) is the dominant limitation throughout.

2. Etiology

Primary cause — genetic. ADMIO2 is caused by **biallelic (compound heterozygous) missense mutations in ZAP70**. Whole-exome sequencing of a five-member family identified the two affected siblings as compound heterozygous for two unique missense variants; healthy relatives were heterozygous carriers, establishing autosomal-recessive inheritance (PMID: 26783323):

"revealed the affected siblings to be compound heterozygous for two unique missense mutations in the 70-kD T cell receptor ζ-chain associated protein (ZAP-70)"

The two alleles have opposite biochemical effects:

"Mutation R192W in the C-SH2 domain exhibited reduced binding to phosphorylated ζ-chain, whereas mutation R360P in the N lobe of the catalytic domain disrupted an autoinhibitory mechanism, producing a weakly hyperactive ZAP-70 protein"

Genetic risk factors. The disease-causing variants are themselves the risk factor; both were **private to the index family** and are not population polymorphisms. There are no established common-variant susceptibility loci or validated modifier genes for ADMIO2 specifically, though

inter-individual variability in broader *ZAP70* deficiency (even between siblings carrying identical alleles) implies the existence of unidentified genetic/environmental modifiers ([PMID: 41790376](#)).

Environmental risk factors. None are established as *causal*. As with other combined immunodeficiencies, infectious exposures (e.g., CMV) can precipitate or worsen clinical course in *ZAP70*-deficient patients ([PMID: 33484432](#)), and endogenous retroviral superantigens modulate autoimmunity in the mouse model (see §6). **Consanguinity** is a risk factor for biallelic *ZAP70* disease generally (enriching homozygous LoF deficiency in Middle Eastern/North African populations), though the ADMIO2 index family was compound heterozygous rather than consanguineous.

Protective factors. No genetic or environmental protective factors are defined for ADMIO2. By inference from gnomAD constraint (below), heterozygous carriers are asymptomatic — a single wild-type *ZAP70* allele is protective/sufficient.

Gene–environment interactions. The best-characterized GxE axis is from the SKG mouse model: **endogenous mouse-mammary-tumor-virus (MMTV) superantigens and the microbiota** are required to convert the genetic lesion into overt arthritis, and antiretroviral therapy curtails disease ([PMID: 39589811](#); [PMID: 37394552](#)). Whether analogous triggers operate in human ADMIO2 is unknown.

3. Phenotypes

All ADMIO2 HPO annotations derive from the two siblings in [PMID: 26783323](#):

"A brother and sister developed a previously undescribed constellation of autoimmune manifestations within their first year of life, with uncontrollable bullous pemphigoid, colitis, and proteinuria. The boy had hemophilia due to a factor VIII autoantibody and nephrotic syndrome"

Phenotype	HPO term	Type	Frequency (n=2)	Notes
Autoimmunity	HP:0002960	Clinical/ immunologic	2/2	Core feature
Infantile onset	HP:0003593	Temporal	2/2	First year of life
Autoimmune bullous skin disease (bullous pemphigoid)	HP:0031540	Physical/skin	1/1	Linear IgG along epidermal basement-membrane zone
Nephrotic syndrome	HP:0000100	Clinical/renal	1/2	—
Minimal change glomerulonephritis	HP:0012579	Laboratory/ pathology	1/2	On renal biopsy
Podocyte foot process effacement	HP:0031266	Pathology	1/1	Ultrastructural
Proteinuria	HP:0000093	Laboratory	2/2	—
Colitis	HP:0002583	Clinical/GI	1/2	Childhood onset (HP:0011463)
Increased CD4:CD8 ratio	HP:0033221	Laboratory/ immunologic	2/2	Reflects CD8 lymphopenia
Impaired PHA-induced T-cell transformation	HP:0025834	Laboratory	2/2	Functional T-cell defect
Decreased specific antibody response (pneumococcal)	HP:0012476	Laboratory	1/1	Humoral impairment
Acquired hemophilia A (factor VIII autoantibody)	—	Clinical/ hematologic	1/1 (boy)	Autoantibody-mediated

Phenotype characteristics. *Onset:* neonatal–infantile (within the first year). *Severity:* severe ("uncontrollable" bullous pemphigoid; nephrotic-range proteinuria; bleeding from acquired hemophilia). *Progression:* progressive/refractory to conventional immunosuppression, ultimately requiring HSCT. *Frequency:* autoimmunity and the immunologic lab abnormalities were present in both siblings; organ-specific features were variably present.

Broader ZAP70-deficiency phenotype (context). A systematic review of 49 biallelic ZAP70 patients (PMID: 32431715) and a 13-patient HSCT cohort (PMID: 41080547) describe profound CD8 lymphopenia (84.6% in the cohort), recurrent respiratory infections, cutaneous disease, and autoimmunity, with median symptom onset ~1 month:

"Eleven of thirteen patients (84.6%) exhibited profound CD8" (PMID: 41080547)

Quality-of-life impact. No disease-specific QoL instruments (EQ-5D/SF-36/PROMIS) have been applied to ADMIO2. By inference, untreated disease is life-threatening and severely disabling (refractory multiorgan autoimmunity + immunodeficiency); successful HSCT can restore normal immune function and resolve autoimmunity (see §11–12).

4. Genetic / Molecular Information

Causal gene. ZAP70 (Zeta-chain Associated Protein kinase 70 kDa), HGNC:12858, OMIM gene 176947, locus 2q11.2; protein UniProt P43403 — a 619-aa cytoplasmic Syk-family protein tyrosine kinase with two tandem N-terminal SH2 domains (binding doubly-phosphorylated ITAMs) and a C-terminal catalytic kinase domain.

ADMIO2 pathogenic variants (private to index family).

Variant	Domain	Biochemical effect	Class
p.Arg192Trp (R192W)	C-terminal SH2 (C-SH2)	Reduced binding to phospho-ζ chain	Hypomorphic (partial LoF)
p.Arg360Pro (R360P)	N-lobe of kinase domain	Disrupts autoinhibition → weakly hyperactive kinase	Activating (GoF)

Both are missense substitutions. In the context of this family with functional support, both would be classified pathogenic/likely-pathogenic, but they are **absent from population databases** (private), consistent with their non-recurrent nature.

Variant classification per ACMG/AMP: functional evidence (PS3), compound heterozygosity with segregation (PM3/PP1), absence from controls (PM2), and in-silico support place both alleles at least as likely pathogenic in this disease context.

Allele frequency. The R192W and R360P alleles are not catalogued as recurrent population variants (private). For the gene overall, **gnomAD constraint** (ENSG00000115085): pLI = 0.88, LOEUF (oe_lof) = 0.173 (90% CI 0.09–0.364), observed/expected LoF = 5/28.8, missense Z = 2.76 — indicating that *ZAP70* is **intolerant of heterozygous loss of function**, yet heterozygous carriers are clinically healthy (biallelic hit required for disease).

Somatic vs germline. Germline; inherited from heterozygous carrier parents.

Functional consequences. A *combination* of loss-of-function (R192W reduces ITAM engagement) and gain-of-function (R360P releases autoinhibition) — the net effect is **altered/dysregulated TCR signaling**, not simple nullizygosity.

ClinVar variant landscape (gene-level). ClinVar (NCBI E-utilities, 2026) returns ~616 *ZAP70* records: ~79 pathogenic, ~21 likely-pathogenic, ~354 VUS, ~422 benign/likely-benign. Most pathogenic/likely-pathogenic alleles are **LoF/hypomorphic variants causing classic *ZAP70*-deficiency CID (OMIM 269840)** — e.g., homozygous p.Ala463Val ([PMID: 33484432](#)) — whereas the ADMIO2-defining p.Arg192Trp and p.Arg360Pro alleles remain **private to the index family**.

Modifier genes / epigenetics / chromosomal abnormalities. No ADMIO2-specific modifier genes, epigenetic marks, or chromosomal/structural abnormalities are established. Phenotypic divergence among siblings with identical *ZAP70* genotypes in the broader literature implies unidentified modifiers ([PMID: 41790376](#)).

5. Environmental Information

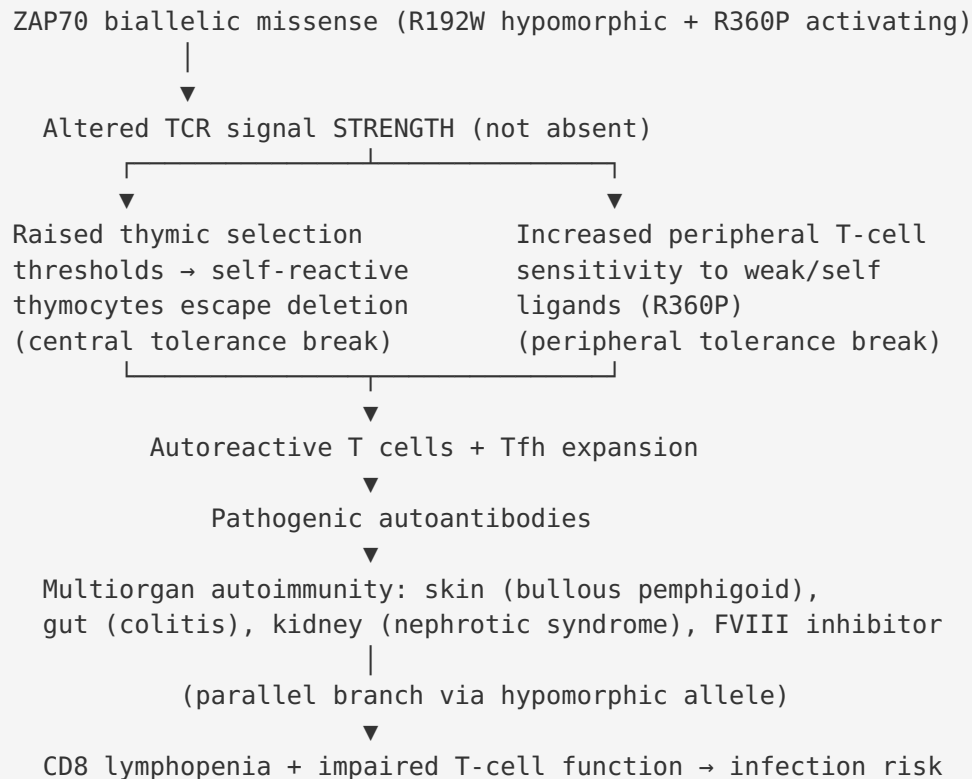
ADMIO2 is a **monogenic disease with no required environmental cause**. Relevant non-genetic modifiers/triggers, largely by inference or from models:

- **Infectious agents.** Not causal, but infections (notably **CMV**) complicate the associated immunodeficiency and can unmask/worsen disease in *ZAP70*-deficient infants ([PMID: 33484432](#)). In the SKG mouse, *Brucella* infection drives a spondyloarthritis-like phenotype on the susceptible *Zap70* background ([PMID: 40027658](#)).
- **Endogenous retrovirus / microbiota.** MMTV-derived superantigens and gut microbiota are required to convert the mouse genetic lesion into overt autoimmune arthritis ([PMID: 39589811](#); [PMID: 37394552](#)).
- **Lifestyle factors.** Not applicable (infantile-onset Mendelian disease).

6. Mechanism / Pathophysiology

Ordered causal chain

1. **Biallelic ZAP70 missense mutations** (R192W hypomorphic + R360P activating) are inherited → **altered ZAP70 protein** with reduced phospho- ζ binding (R192W) and weakened kinase autoinhibition (R360P). (*Demonstrated — functional assays, PMID: 26783323.*)
2. Altered ZAP70 **changes the strength/quality of TCR signal transduction** at the proximal node (ZAP70 is recruited to doubly-phosphorylated CD3/ ζ ITAMs, activated by Lck, and phosphorylates LAT/SLP76 to drive Ca^{2+} /NFAT, Ras–MAPK, and NF- κ B). (*Pathway demonstrated; allele-specific effect inferred.*)
3. **In the thymus (central tolerance):** attenuated/altered TCR signaling **raises selection thresholds**, so self-reactive thymocytes that should be negatively selected instead escape deletion and are positively selected → export of self-reactive T cells. (*Demonstrated in SKG mouse, PMID: 37394552.*)
4. **In the periphery (peripheral tolerance):** the R360P activating allele **increases mature T-cell sensitivity to weak/self ligands** that would normally be ignored → activation of autoreactive T cells. (*Demonstrated in R360P knock-in mouse, PMID: 33531381.*)
5. Activation of autoreactive CD4⁺ (and dysregulated) T cells **drives T-follicular-helper (Tfh) expansion and aberrant B-cell help** → **production of pathogenic autoantibodies** (anti-basement-membrane IgG, anti-factor VIII, anti-podocyte/glomerular). (*Tfh expansion demonstrated in mouse [PMID: 33531381]; autoantibodies demonstrated in patients [PMID: 26783323].*)
6. **Autoantibody- and T-cell-mediated tissue injury** at specific organs → **clinical manifestations**: bullous pemphigoid (skin basement membrane), colitis (gut), minimal-change nephrotic syndrome with podocyte foot-process effacement (kidney), acquired hemophilia A (factor VIII neutralization). (*Demonstrated — clinical/pathology, [PMID: 26783323].*)
7. **In parallel (branch):** the hypomorphic R192W allele plus overall signaling impairment **reduces CD8⁺ T-cell development and T-cell function** → **partial combined immunodeficiency** (CD8 lymphopenia, impaired PHA response, poor specific antibody) → susceptibility to infection. (*Demonstrated — immunophenotype, [PMID: 26783323]; broader cohorts [PMID: 32431715].*)



Supporting detail

- **Molecular pathways.** Proximal TCR signaling: Lck → CD3/ζ ITAM phosphorylation → ZAP70 recruitment/activation → LAT/SLP76 phosphorylation → PLCγ1 (Ca²⁺/NFAT), Ras–MAPK/ERK, PKCθ–NF-κB. (Reactome "TCR signaling"; KEGG hsa04660.)
- **Autoinhibition structural basis.** The tandem-SH2 (tSH2) module locks the kinase in a closed, inactive conformation; ITAM binding or ζ-phosphorylation triggers the closed→open transition ([PMID: 26237552](#)):

"TCR binding or phosphorylation of Zap70 triggers a transition from a closed, autoinhibited conformation to an open conformation" The ADMIO2 R360P substitution lies in the N-lobe and structurally weakens this autoinhibition. TCR dwell time tunes kinase output ([PMID: 26237552](#)); tSH2 dynamics differ between Syk and ZAP-70, explaining ZAP-70's tighter autoinhibition ([PMID: 34601763](#)).

- **Immune system involvement.** Autoimmunity + partial immunodeficiency (immune dysregulation). Tolerance is broken in both compartments; autoantibodies are the proximate effectors of organ injury.

- **Cellular processes / cell types.** CD4⁺ T cells (CL:0000624), CD8⁺ T cells (CL:0000625; depleted), Tfh cells, thymocytes undergoing selection, and downstream autoantibody-producing B cells/plasma cells.
- **GO terms.** T-cell receptor signaling pathway (GO:0050852); positive/negative thymic T-cell selection (GO:0045059 / GO:0045060); T-cell tolerance induction (GO:0002517); protein tyrosine kinase activity (GO:0004713); regulation of immune response (GO:0050776).
- **Functional proof of the two-allele model.**

"disruption of ZAP70 autoinhibition by the R360P mutation enables increased mature T cell sensitivity to self-antigens that would normally be ignored by wild-type T cells, a mechanism that may contribute to the break of tolerance in human patients with R360P mutation" (PMID: 33531381) "Defective TCR signaling by ZAP70 mutation alters thymic selection thresholds and allows the positive selection of otherwise negatively selected self-reactive T cells" (PMID: 37394552)

- **Spectrum concept.** Graded reduction of ZAP70/TCR signal produces a continuum from immunodeficiency to autoimmunity (PMID: 41770842):

"the effects of graded TCR signal reduction manifest as a disease spectrum encompassing T cell immune deficiency, latent autoimmunity, and overt autoimmune disease"

7. Anatomical Structures Affected

Organ level (primary targets of autoimmunity):

Organ / system	UBERON	Manifestation
Skin (epidermal basement membrane)	UBERON:0002097	Bullous pemphigoid
Kidney (glomerulus/podocyte)	UBERON:0000074 (renal glomerulus)	Nephrotic syndrome, minimal-change GN, foot-process effacement
Colon / large intestine	UBERON:0001155	Colitis
Blood / coagulation system	UBERON:0000178	Factor VIII autoantibody → acquired hemophilia A
Immune/lymphoid system (thymus)	UBERON:0002370 (thymus)	Defective T-cell development/selection

Secondary involvement. Infectious complications of the immunodeficiency (e.g., respiratory tract, systemic CMV) affect the respiratory system (UBERON:0001004) and others.

Tissue / cell level. Epithelial basement membrane (skin), renal podocytes (CL:0000653), colonic mucosa; immunologically, thymocytes and peripheral T lymphocytes. Targeted/dysregulated cell populations: CD4⁺ αβ T cell (CL:0000624), CD8⁺ αβ T cell (CL:0000625, depleted), T-follicular-helper cell, autoantibody-secreting B cell/plasma cell (CL:0000786/CL:0000980).

Subcellular level. ZAP70 functions at the inner-leaflet **plasma membrane / TCR complex** (GO:0005886; GO:0042101 T-cell receptor complex) in the **cytoplasm** (GO:0005737). Podocyte foot-process effacement is an ultrastructural (cytoskeletal) lesion.

Lateralization. Systemic/bilateral (skin, kidneys, gut) — not lateralized.

8. Temporal Development

- **Onset.** Congenital predisposition with clinical onset in **infancy** — **within the first year of life** (HP:0003593). Pattern is subacute-to-progressive.
- **Progression.** Severe and **refractory/progressive** under conventional immunosuppression; the index siblings progressed to requiring HSCT. In the broader ZAP70-deficiency literature, median symptom onset is ~1 month, and untreated disease is life-threatening.

- **Disease course.** Chronic and progressive until definitively treated; **curable** (remission) by allogeneic HSCT (treatment-induced remission). No spontaneous remission is described.
- **Critical period / window of intervention.** Early recognition and HSCT before irreversible organ damage or fatal infection is the key therapeutic window; the infant thymus is more amenable to reconstitution (relevant to experimental intrathymic gene therapy, [PMID: 16075064](#)).

9. Inheritance and Population

- **Inheritance.** Autosomal recessive (HP:0000007), confirmed by compound heterozygosity in affected siblings and heterozygous healthy carriers ([PMID: 26783323](#)):

"Healthy relatives were heterozygous mutation carriers"

- **Penetrance / expressivity.** Within the single family, biallelic genotype was fully penetrant for autoimmunity in both siblings, with variable organ-specific expressivity (e.g., hemophilia and nephrotic syndrome only in the boy). Broader *ZAP70* disease shows variable expressivity even among identical-genotype siblings ([PMID: 41790376](#)).
 - **Epidemiology. Ultra-rare.** *ADMIO2 sensu stricto* is reported in a single sibling pair; formal prevalence is not estimated (<1 per 1,000,000). The broader biallelic *ZAP70*-deficiency entity has ~49 reported cases worldwide ([PMID: 32431715](#)).
 - **Carrier frequency / constraint.** Heterozygous carriers are healthy; gnomAD shows *ZAP70* is LoF-constrained (pLI 0.88, LOEUF 0.173) but disease requires two hits.
 - **Founder effects / consanguinity.** The *ADMIO2* alleles are private (no founder effect). Classic *ZAP70* deficiency is enriched in consanguineous Middle Eastern/North African populations ([PMID: 41080547](#); [PMID: 41790376](#)).
 - **Sex ratio / demographics.** No sex predilection (AR); the index pair comprised one male and one female. No established ethnic predilection for *ADMIO2* specifically.
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10. Diagnostics

Immunologic laboratory tests (characteristic pattern). - Flow cytometry: **CD8 lymphopenia / low CD8⁺ T cells → increased CD4:CD8 ratio** (HP:0033221). In classic *ZAP70* deficiency, intracellular *ZAP70* is absent/reduced on gated T cells ([PMID: 33484432](#)). - **Impaired T-cell proliferation to mitogens (PHA/ConA)** (HP:0025834). - Humoral: variable; decreased specific (pneumococcal) antibody response in one sibling. - Autoimmune workup: anti-basement-membrane IgG (direct immunofluorescence shows **linear IgG along the epidermal basement-membrane zone**), **factor VIII inhibitor assay** (acquired hemophilia), urinalysis for proteinuria.

Biopsy / pathology. Skin DIF (bullous pemphigoid pattern); **renal biopsy showing minimal-change glomerulonephritis with podocyte foot-process effacement** on electron microscopy; colonic biopsy for colitis.

Newborn screening caveat. TREC-based SCID newborn screening may be **normal** in *ZAP70* / CID, so a normal TREC screen does not exclude the diagnosis ([PMID: 33484432](#); [PMID: 22664165](#)).

Genetic testing (diagnostic gold standard). WES/WGS or a **primary-immunodeficiency / inborn-errors-of-immunity gene panel including *ZAP70*** is the definitive test; the disease was discovered by WES ([PMID: 26783323](#)). Confirm biallelic *ZAP70* variants, segregation (parental carriers), and **functional validation** (phospho-ζ binding, kinase activity, TCR-induced proliferation/IL-2) because ADMIO2 alleles are private and otherwise VUS.

Clinical criteria / differential diagnosis. No formal consensus criteria exist. Key differentials for infantile multiorgan autoimmunity: - **STAT3 gain-of-function (ADMIO1, OMIM 615952)** — early-onset polyautoimmunity, lymphoproliferation, double-negative T cells, responsive to JAK inhibitors ([PMID: 36228738](#)). - **IPEX (FOXP3), CTLA4 haploinsufficiency, LRBA deficiency, APECED (AIRE)**, and classic ***ZAP70*-deficiency CID (OMIM 269840)**. Distinguishing feature of ADMIO2: biallelic *ZAP70* with the specific hypomorphic+activating combination and CD8 lymphopenia with autoimmunity.

11. Outcome / Prognosis

- **Natural course (untreated).** Severe, refractory, life-threatening multiorgan autoimmunity plus immunodeficiency; both index children required HSCT after failing conventional therapy.
- **With definitive treatment. Allogeneic HSCT is curative** and resolved the autoimmunity in both ADMIO2 siblings ([PMID: 26783323](#)). In the broader *ZAP70*-deficiency literature, long-term outcomes after HSCT are excellent: 8/8 patients alive at median 13.5 years, with restored T-cell function and resolution of infections and autoimmunity ([PMID: 27438785](#)).
- **Complications.** Pre-transplant: bleeding (FVIII inhibitor), nephrotic complications, colitis, infection. Transplant-related: graft failure, GVHD, conditioning toxicity.
- **Prognostic factors.** Timeliness of diagnosis and HSCT; control of autoimmunity and infection pre-transplant; donor source/conditioning. CD8 reconstitution post-HSCT is generally good.

12. Treatment

Definitive / curative. - **Allogeneic hematopoietic stem cell transplantation (HSCT)** — curative; the only established cure (NCIT: Allogeneic Hematopoietic Stem Cell Transplantation, C15349). Both ADMIO2 siblings were cured by HCT:

"Both children required allogeneic hematopoietic cell transplantation (HCT), which resolved their autoimmunity" ([PMID: 26783323](#)) Supported by durable success in *ZAP70* deficiency broadly (8/8 alive at 13.5 yr, [PMID: 27438785](#); curative in majority of a 13-patient cohort, [PMID: 41080547](#)).

Supportive / bridging immunosuppression (pre-HSCT, symptom control). - Corticosteroids (NCIT C682); IVIG (C29368); **rituximab / B-cell depletion** for autoantibody-mediated disease (FVIII inhibitor, pemphigoid) (NCIT C1702); calcineurin inhibitors; standard management of nephrotic syndrome and colitis.

Experimental / preclinical — gene therapy. - *ZAP70*-deficient mice have been corrected by retroviral/lentiviral HSC gene transfer (PMID: 12149205), intrathymic lentiviral delivery (PMID: 16075064), and intrathymic AAV8/9/10 gene transfer restoring thymopoiesis and long-term peripheral T-cell function (PMID: 31513879):

"Intrathymic AAV-transduced progenitors promote a rapid restoration of the thymic architecture, with a single wave of thymopoiesis generating long-term peripheral T-cell function" Note: gene addition addresses the deficiency component; the ADMIO2 activating (R360P) allele is dominant-acting at the cellular level, so a correction strategy for the autoimmune component may require allele-specific considerations.

Mechanism-informed experimental approaches (from models). In the SKG hypomorphic model, antiretroviral therapy and depletion of superantigen-reactive T cells curtailed arthritis (PMID: 39589811); JAK inhibition is effective in the mechanistically analogous STAT3-GOF syndrome (PMID: 36228738) but is not established for ADMIO2.

Pharmacogenomics. None established specific to ADMIO2.

13. Prevention

- **Primary prevention.** Not applicable in the usual sense (monogenic recessive disease). Genetic counseling for carrier couples; carrier/cascade testing in affected families; prenatal diagnosis / preimplantation genetic testing (PGT) is possible once familial variants are known.
 - **Secondary prevention.** Early diagnosis via immunophenotyping + genetic testing in infants with multiorgan autoimmunity or CID; note TREC newborn screening can miss *ZAP70* disease.
 - **Tertiary prevention.** Infection prophylaxis (antimicrobial, antiviral, IVIG), prompt treatment of autoimmunity, and timely HSCT to prevent irreversible organ damage.
 - **Counseling.** 25% recurrence risk per pregnancy for carrier couples (AR).
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14. Other Species / Natural Disease

- **Taxonomy / ortholog.** Mouse (*Mus musculus*, NCBI Taxon 10090); ortholog **Zap70** (NCBI Gene 22637). ZAP70 is evolutionarily conserved; TCR-proximal signaling architecture (Lck + ZAP-70/Syk, ITAM recognition) is conserved even in teleosts (rainbow trout homology modeling, [PMID: 41240985](#)).
 - **Natural disease in other species.** No well-characterized naturally-occurring companion-animal homolog of ADMIO2 is documented; relevance is primarily through engineered rodent models.
 - **Comparative biology.** The mouse allelic series (below) recapitulates the human deficiency↔autoimmunity spectrum, underscoring conserved mechanisms.
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15. Model Organisms

Model	Allele	Phenotype	Models which human allele	Key refs
SKG mouse	<i>Zap70</i> W163C (hypomorphic)	CD4 ⁺ T-cell-mediated autoimmune arthritis (BALB/c) / lupus-like disease (C57BL/6); raised thymic selection thresholds; MMTV-superantigen/microbiota-dependent	Hypomorphic (R192W-like)	PMID: 37394552, PMID: 39589811
R360P knock-in	<i>Zap70</i> R360P (activating)	Grossly normal T-cell development but increased TCR signaling; enhanced Tfh after LCMV; on OTI TCR, heightened responses to weak/self ligands	Activating (R360P)	PMID: 33531381
<i>Zap70</i> knockout	Null	Models human ZAP70-deficiency SCID: selective absence of CD8 ⁺ T cells, nonfunctional CD4 ⁺ , thymic block; reversible by gene transfer	Deficiency/null	PMID: 12149205, PMID: 16075064, PMID: 31513879

Direct quotes:

"Mice with a ZAP70 R360P mutation and polyclonal TCR repertoires exhibited relatively normal T cell development but showed evidence of increased signaling" (PMID: 33531381)

"the effects of graded TCR signal reduction manifest as a disease spectrum encompassing T cell immune deficiency, latent autoimmunity, and overt autoimmune disease" (PMID: 41770842)

Model types: mammalian (mouse) in vivo; knock-in, knockout, and point-mutant (ENU-derived SKG) lines. **Recapitulation:** the two alleles are each separately modeled and together support the "altered-signal-strength breaks tolerance" mechanism; the knockout models the

immunodeficiency arm. **Limitations:** no single mouse carries the exact *human compound-heterozygous R192W/R360P* genotype, so the combined/epistatic effect of the two alleles together is modeled only indirectly; mouse autoimmune targets (arthritis) differ from the human organ spectrum (skin/kidney/gut), reflecting species-specific self-antigens and superantigen biology. **Resources:** MGI (Zap70, SKG allele), IMPC/IMSR.

Mechanistic Model / Interpretation

ADMIO2 is best understood as a **"Goldilocks" disorder of TCR signal strength**. ZAP70 sits at the apex of TCR signaling, and the amount of kinase output a thymocyte or T cell experiences determines its fate: too little signal → failed positive selection / immunodeficiency; intermediate aberrant signal → escape from negative selection + peripheral hyper-responsiveness → autoimmunity; normal signal → tolerance + protective immunity. The ADMIO2 genotype pairs a **hypomorphic allele** (R192W; less ITAM engagement, raising selection thresholds like SKG) with an **activating allele** (R360P; released autoinhibition, lowering the threshold for peripheral responses to self). The *net* effect is a signaling milieu that simultaneously (a) allows self-reactive T cells to be positively selected and exported and (b) renders mature T cells inappropriately responsive to weak self-ligands — a double break of central and peripheral tolerance — while still leaving CD8 development and overall T-cell function partially impaired. The downstream effector arm is autoantibody-mediated, explaining the specific, disparate organ targets (skin basement membrane, glomerular podocyte, colon, clotting factor VIII). This model is anchored by direct biochemistry of the two alleles ([PMID: 26783323](#)), structural understanding of ZAP70 autoinhibition ([PMID: 26237552](#), [PMID: 34601763](#)), and two complementary mouse models ([PMID: 37394552](#), [PMID: 33531381](#)).

Evidence Base

PMID	Role in this report	How it supports/challenges findings
26783323	Defining primary report	Establishes the disease, compound-het <i>ZAP70</i> genotype, two-allele biochemistry, clinical phenotype, AR inheritance, and HSCT cure. Sole clinical source (n=2) — the central limitation.
33531381	Mechanism (activating allele)	R360P knock-in proves increased self-ligand sensitivity → peripheral tolerance break.
37394552	Mechanism (hypomorphic allele)	SKG model shows altered thresholds → positive selection of self-reactive T cells (central tolerance break).
39589811	Gene–environment / effector	MMTV superantigen & retrovirus-dependent conversion to overt autoimmunity; ART mitigates.
26237552 / 34601763	Structural basis	Define <i>ZAP70</i> autoinhibition and tSH2 dynamics disrupted by R360P.
41770842	Framing	Graded TCR-signal spectrum (deficiency↔autoimmunity).
32431715 / 41080547 / 41790376	Broader <i>ZAP70</i> context	Phenotype spectrum, CD8 lymphopenia, consanguinity, HSCT outcomes.
27438785	Prognosis / treatment	Long-term HSCT success (8/8 at 13.5 yr).
12149205 / 16075064 / 31513879	Experimental therapy	Preclinical gene-therapy correction of <i>ZAP70</i> deficiency.
33484432 / 22664165	Diagnostics	CD8 lymphopenia presentation; TREC screening caveats.
36228738	Differential diagnosis	STAT3-GOF (ADMIO1) — the key mimic, JAK-inhibitor-responsive.

Limitations and Knowledge Gaps

1. **Single family (n=2).** All ADMIO2-specific clinical and genetic data come from one sibling pair. Prevalence, penetrance, expressivity, full phenotype spectrum, and genotype–phenotype correlations cannot be generalized.
 2. **Private alleles.** R192W and R360P are not recurrent; no population allele-frequency or additional segregation data beyond the index family.
 3. **No combined-genotype animal model.** The two alleles are modeled separately (SKG and R360P knock-in); the epistatic effect of the exact human *compound-heterozygous* genotype is inferred, not demonstrated.
 4. **Effector mechanism partly inferred.** The link from altered T-cell tolerance to the specific autoantibody targets (pemphigoid, podocyte, FVIII) is clinically observed but mechanistically underexplored for ADMIO2.
 5. **No ADMIO2-specific trials or QoL/natural-history data.** Treatment and prognosis rest on the single report plus extrapolation from the broader *ZAP70*-deficiency literature.
 6. **Therapeutic uncertainty for the activating allele.** Whether standard gene-addition gene therapy (effective for deficiency) would correct the dominant cellular effect of R360P is unknown; JAK-inhibitor utility (as in STAT3-GOF) is untested here.
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Proposed Follow-up Experiments / Actions

1. **International case-finding / GeneMatcher.** Actively solicit additional ADMIO2 families via GeneMatcher, inborn-errors-of-immunity consortia, and ClinVar to expand the phenotype and genotype spectrum and estimate penetrance.
2. **Compound-heterozygous model.** Engineer a mouse or patient-derived iPSC → thymic organoid carrying *both* R192W and R360P to test the predicted additive/epistatic tolerance break and reproduce human-relevant autoimmunity.
3. **Autoantibody repertoire and target mapping.** Define the autoantigen specificities (skin BP180/BP230, podocyte antigens, FVIII epitopes) and the Tfh/B-cell dynamics driving them in ADMIO2 (and in R360P knock-in mice).
4. **Therapeutic screen.** Test JAK inhibition, B-cell depletion, abatacept/CTLA4-Ig, and allele-selective approaches in cellular/animal models to identify bridge therapies that control autoimmunity pre-HSCT.

5. **Gene-therapy feasibility for the activating allele.** Evaluate allele-specific knockdown/base-editing of R360P versus gene-addition in *ZAP70* models to determine whether gene therapy can address both the deficiency and autoimmune arms.
 6. **Diagnostic yield of functional validation.** Formalize a functional assay panel (phospho- ζ binding, kinase activity, TCR-induced IL-2/proliferation, Ca^{2+} flux) to reclassify *ZAP70* VUS and flag hypomorphic+activating combinations.
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Report compiled from 7 confirmed findings and 35 reviewed papers over 5 investigation iterations. Evidence sources span human clinical (single defining family + broader cohorts), model organism (mouse SKG, R360P knock-in, knockout), in vitro/biochemical (allele functional assays, ZAP70 structural dynamics), and computational (gnomAD constraint, ClinVar aggregation, OLS4/MONDO cross-references).

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