Syndromic Multisystem Autoimmune Disease Due to ITCH Deficiency — Comprehensive Research Report

Disease: Syndromic Multisystem Autoimmune Disease Due to ITCH Deficiency **MONDO ID:** MONDO:0013245 · **OMIM:** #613385 · **Orphanet:** ORPHA:228426 · **GARD:** 0010775 **Causal gene:** ***ITCH*** (itchy E3 ubiquitin protein ligase; HGNC:13890; NCBI Gene 83737; UniProt Q96J02; 20q11.22) **Category:** Mendelian, autosomal recessive

> Note: the gene symbol *ITCH* derives from the "itchy" mouse and should not be confused with pruritus or other "itch" phenotypes. The identifiers above (MONDO:0013245, OMIM 613385, gene *ITCH* on chr20) define this entry.

Summary

Syndromic multisystem autoimmune disease due to ITCH deficiency is an autosomal-recessive primary immune-regulatory disorder caused by biallelic loss-of-function variants in *ITCH*, the gene encoding the itchy E3 ubiquitin protein ligase — a NEDD4-family HECT-domain enzyme located at chromosome 20q11.22. The condition was first defined in 2010 in a large Old Order Amish kindred, in which autozygosity mapping linked the phenotype to chromosome 20 and identified a homozygous truncating *ITCH* mutation (the founder frameshift allele c.378_394del) in ten affected patients (PMID: 20170897). The disorder carries the synonyms **"Autoimmune Disease, Multisystem, with Facial Dysmorphism (ADMFD)"** and **"ITCH E3 ubiquitin ligase deficiency."**

Mechanistically, ITCH is an E3 ubiquitin ligase that enforces peripheral T-cell tolerance. It ubiquitylates and degrades a defined set of substrates — JunB, c-Jun, Notch, p63/p73, c-FLIP and TIEG1 — and participates in the A20 (TNFAIP3)/TAX1BP1 ubiquitin-editing complex that restrains NF-κB signaling. When ITCH is absent, these brakes fail: JunB accumulates and drives Th2 skewing, T cells cannot be rendered anergic, TGF-β/Foxp3-dependent regulatory T-cell generation is impaired, and NF-κB signaling is disinhibited. The net result is early-onset,

progressive, multi-organ autoimmunity — autoimmune hepatitis, enteropathy, chronic interstitial lung disease, thyroiditis, type 1 diabetes, myositis and arthritis — layered on a syndromic background of failure to thrive, facial dysmorphism and developmental delay.

The disease has high morbidity and mortality. Management rests on broad immunosuppression for individual autoimmune manifestations, but the only reported disease-modifying/curative therapy is **allogeneic hematopoietic stem cell transplantation (HSCT)**, which produced durable multisystem remission at three years in a severely affected patient (PMID: 42148098). The **itchy / non-agouti-lethal 18H (a18H) mouse**, in which a paracentric inversion disrupts *Itch*, faithfully recapitulates the human multi-organ immunopathology and remains the principal model organism. A 2022 report also expanded the phenotype to include a cellular mitochondrial bioenergetic defect (PMID: 36338154).

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1. Disease Information

Overview. ITCH deficiency is a rare monogenic syndrome combining systemic autoimmunity with dysmorphic and developmental features. Affected children typically present in infancy or early childhood with failure to thrive, distinctive facial dysmorphism, developmental delay, and organ-specific autoimmune disease that accrues over time. The original description emphasized that patients "not only have multisystem autoimmune disease but also display morphologic and developmental abnormalities" (PMID: 20170897), i.e., the disorder is *syndromic* rather than a pure immune dysregulation phenotype.

Key identifiers (verified cross-references for MONDO:0013245).

Resource	Identifier
MONDO	MONDO:0013245
OMIM	#613385
Orphanet	ORPHA:228426
GARD	0010775
MedGen / UMLS	C3150649 (MedGen 461999)
NANDO	2200739
ICD-11 (foundation)	1970749000
Causal gene (HGNC)	HGNC:13890 (*ITCH*)
NCBI Gene	83737
Ensembl	ENSG00000078747

Synonyms / alternative names. "Autoimmune disease, multisystem, with facial dysmorphism (ADMFD)"; "ITCH E3 ubiquitin ligase deficiency"; "ITCH deficiency"; "syndromic multisystem autoimmune disease due to ITCH deficiency."

Source of information. The knowledge base entry is derived from aggregated disease-level resources (OMIM, Orphanet, MONDO) combined with individual-patient case reports and small case series (the original Amish cohort of 10 patients; subsequent White British, Black German, and other individual patients). There is no large EHR-derived or registry dataset for this ultra-rare disease — knowledge is derived from **individual patient reports and functional studies**, supplemented by the *Itch*-null mouse and in-vitro biochemistry.

2. Etiology

Primary cause — genetic. The disease is caused by biallelic (homozygous or compound-heterozygous) loss-of-function variants in *ITCH*. The founding event in the Amish population is a homozygous truncating frameshift (c.378_394del, p.Lys126fs). Other patients carry two novel variants resulting in complete absence of ITCH protein in fibroblasts (PMID: 20170897; PMID: 36338154).

Genetic risk factors. The disorder is Mendelian; the causal risk factor is inheritance of two pathogenic *ITCH* alleles. In the Amish founder population, the single frameshift allele segregates at elevated frequency; **consanguinity** and membership in a genetically isolated founder population are the dominant risk-conferring circumstances. Carrier (heterozygous) status is not known to cause disease.

Environmental risk factors. None established as causal. Because the phenotype is autoimmune, environmental immune triggers (infections, antigenic exposures) plausibly modulate the timing or severity of specific autoimmune flares, but no specific environmental factor has been demonstrated. Age (young) and the autoimmune milieu influence expression; a firm sex predominance has not been established in this small cohort.

Protective factors. No genetic or environmental protective factors have been identified for this monogenic recessive disease (not applicable in the usual GWAS/epidemiological sense).

Gene–environment interactions. Mechanistically, loss of ITCH removes a tolerance checkpoint, so ordinary antigenic/environmental stimuli that would normally be tolerized instead provoke autoimmunity. In the mouse model, high-dose tolerizing antigen **failed** to block airway inflammation in *Itch*$^{-/-}$ animals (PMID: 16557301) — a direct demonstration that the genetic lesion reprograms the response to an environmental (antigen) exposure. No formal human GxE data exist.

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3. Phenotypes

ITCH deficiency is a multisystem disorder. The table below summarizes the principal phenotypes compiled from the original Amish series and subsequent case reports, with suggested HPO terms.

Phenotype	Type	Onset	Frequency (qualitative)	Suggested HPO term
Failure to thrive / growth failure	Physical / constitutional	Infancy	Common (core feature)	HP:0001508
Dysmorphic facial features	Physical	Congenital	Common (core feature)	HP:0001999
Developmental delay	Neurodevelopmental	Infancy/ childhood	Common (core feature)	HP:0001263
Autoimmune hepatitis	Clinical sign / lab	Childhood	Frequent; can cause acute liver failure	HP:0001409 (hepatitis) + HP:0002960 (autoimmunity)
Chronic interstitial lung disease	Clinical sign	Childhood	Severe cases (tracheostomy, ventilation)	HP:0006530
Enteropathy / chronic diarrhea	Clinical sign	Childhood	Frequent	HP:0004386
Thyroiditis (autoimmune)	Lab / clinical	Childhood	Reported	HP:0100646
Type 1 diabetes mellitus	Lab / clinical	Childhood	Reported	HP:0100651
Juvenile polymyositis / myositis	Clinical sign	Childhood	Reported	HP:0003198
Inflammatory (autoimmune) arthritis	Clinical sign	Childhood	Reported	HP:0001369
Psoriasis	Physical / skin	Childhood	Reported	HP:0003765
Sjögren's-like parotitis	Clinical sign	Childhood	Reported	HP:0030149 (parotitis)

Phenotype	Type	Onset	Frequency (qualitative)	Suggested HPO term
Immune / autoimmune neutropenia	Lab	Childhood	Reported	HP:0001882

Characteristics. Onset is early (neonatal to early childhood) with an **insidious-then-progressive** course: the syndromic features (failure to thrive, dysmorphism, developmental delay) are present early, and autoimmune organ involvement accumulates over time. Severity ranges from moderate to severe/life-threatening, with autoimmune hepatitis capable of progressing to acute liver failure (PMID: 30705142) and chronic lung disease requiring tracheostomy and long-term ventilation (PMID: 42148098). Expressivity is variable even among patients sharing the same genotype.

Quality-of-life impact. Severe. Chronic ventilator dependence, recurrent autoimmune flares, hepatic and gastrointestinal dysfunction, developmental delay and failure to thrive collectively impose a very high burden on daily functioning. No disease-specific EQ-5D/SF-36/PROMIS data exist for this ultra-rare condition.

4. Genetic / Molecular Information

Causal gene. *ITCH* (itchy E3 ubiquitin protein ligase), HGNC:13890, OMIM *606409, NCBI Gene 83737, Ensembl ENSG00000078747, located at 20q11.22. RefSeq transcript NM_031483.7; protein UniProt Q96J02, 903 amino acids.

Protein domain architecture. ITCH is a NEDD4-family E3 ligase with: - an N-terminal **C2 domain** (≈ aa 1–115; membrane/Ca^{2+}-phospholipid binding), - four **WW domains** (≈ aa 326–511; substrate recognition via PY motifs), and - a C-terminal catalytic **HECT domain** (≈ aa 569–903; ubiquitin transfer) (PMID: 24787015).

Pathogenic variants. ClinVar pathogenic / likely-pathogenic alleles are overwhelmingly loss-of-function:

Variant (cDNA)	Protein	Class	Note
c.378_394del	p.Lys126fs	Frameshift	**Amish founder allele**
c.1300_1303del	p.Leu434fs	Frameshift	
c.2334del	p.Ile778fs	Frameshift	
—	p.Gln121Ter	Nonsense	
—	p.Trp65Ter	Nonsense	
—	p.Trp555Ter	Nonsense	
—	p.Tyr579Ter	Nonsense	
c.337+1G>A	—	Canonical splice-site	
c.1569+1G>T	—	Canonical splice-site	
c.2214+1G>T	—	Canonical splice-site	
—	p.Met1Ile	Start-loss	

Variant classification & population frequency. Variants are classified pathogenic / likely pathogenic under ACMG/AMP criteria (predicted LOF in a gene with an established LOF disease mechanism). Pathogenic alleles are extremely rare in gnomAD; the Amish frameshift is enriched specifically in that founder population.

Functional consequence. Loss of function. The Amish allele produces a truncated protein (PMID: 20170897); in other patients, ITCH protein is completely absent from fibroblasts (PMID: 36338154). **Somatic vs germline:** germline. **Chromosomal abnormalities:** none required in humans; however, the mouse model arises from a paracentric inversion disrupting *Itch* (see §15).

Modifier genes / epigenetics. No specific human modifier genes or disease-driving epigenetic changes have been defined. Mechanistically ITCH cooperates with Cbl-b/Nedd4 in tolerance circuits (see §6), which could in principle modulate expressivity, but this is not demonstrated for human disease severity.

5. Environmental Information

- **Environmental factors (toxins/radiation/occupational):** none implicated.
- **Lifestyle factors:** none implicated.
- **Infectious agents:** none causal. Infections may act as nonspecific immune triggers, and infectious susceptibility is a clinical concern in immune-dysregulated, immunosuppressed patients, but no pathogen causes or defines the disease.

This is a fundamentally **genetic** disorder; environmental contributions are secondary modulators at most.

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6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation)

1. **Biallelic loss-of-function *ITCH* mutation** (e.g., Amish c.378_394del frameshift) **leads to** absence or truncation of the ITCH HECT-domain E3 ubiquitin ligase. *(Demonstrated — truncated/absent protein in patients.)*
2. Loss of ITCH catalytic activity **results in** failure to ubiquitylate and degrade ITCH substrates — **JunB, c-Jun, Notch, p63/p73, c-FLIP, and TIEG1** — which therefore accumulate. *(Demonstrated for substrates in vitro/mouse.)*
3. **Branch A — Th2 skewing:** accumulation of **JunB** (a Th2-driving transcription factor) **leads to** excessive Th2 differentiation with elevated IL-4, IL-5, IgG1 and IgE. *(Demonstrated in itchy mice.)*
4. **Branch B — failed anergy/tolerance:** loss of ITCH-mediated ubiquitination, which normally converges with **MEKK1–JNK signaling**, **results in** inability to induce T-cell anergy; tolerizing antigen can no longer suppress responses. *(Demonstrated — high-dose antigen fails to tolerize Itch$^{-/-}$ mice.)*
5. **Branch C — deficient Treg generation:** loss of ITCH-mediated monoubiquitination of **TIEG1 leads to** reduced Foxp3 transcription and impaired TGF-β–induced regulatory T-cell generation. *(Demonstrated mechanistically.)*
6. **Branch D — NF-κB disinhibition:** loss of ITCH within the **A20 (TNFAIP3)/TAX1BP1 ubiquitin-editing complex results in** failure to downregulate K63-linked ubiquitination of

TRAF6, **leading to** sustained NF-κB signaling and pro-inflammatory gene expression. *(Demonstrated in the complex; contribution to human disease inferred.)*

7. Branches A–D converge: Th2 skewing + failed anergy + deficient Tregs + NF-κB disinhibition **result in** breakdown of peripheral T-cell tolerance and chronic activation of autoreactive lymphocytes. *(Inferred synthesis.)*
8. Autoreactive, Th2-skewed, poorly regulated lymphocytes **lead to** multi-organ autoimmune attack — liver (autoimmune hepatitis), gut (enteropathy), lung (interstitial inflammation), thyroid, pancreatic islets (T1D), muscle (myositis), joints, skin. *(Demonstrated clinically.)*
9. In parallel/downstream, cellular **mitochondrial bioenergetic dysfunction** (reduced mtDNA copy number, decreased fatty-acid oxidation, oxidative phosphorylation and ATP production) **contributes to** tissue vulnerability and the syndromic growth/developmental features. *(Demonstrated in one patient; relationship to autoimmunity inferred.)*

Supporting detail

Molecular pathways. Ubiquitin–proteasome system (ITCH HECT E3 ligase); TGF-β → TIEG1 → Foxp3 (Treg generation); MEKK1–JNK (anergy); JunB/AP-1 (Th2 transcription); A20/TAX1BP1–TRAF6–NF-κB (innate/inflammatory signaling); Notch signaling (via Notch as an ITCH substrate).

Cellular processes. T-cell differentiation and tolerance (anergy), regulatory T-cell development, Th1/Th2 balance, autophagy regulation (ITCH substrates affect cell fate), inflammation. Suggested **GO** terms: GO:0016567 (protein ubiquitination), GO:0002456 (T cell–mediated immunity), GO:0002667 (regulation of T-cell anergy), GO:0050852 (T cell receptor signaling), GO:0043123 (positive regulation of canonical NF-κB signal transduction).

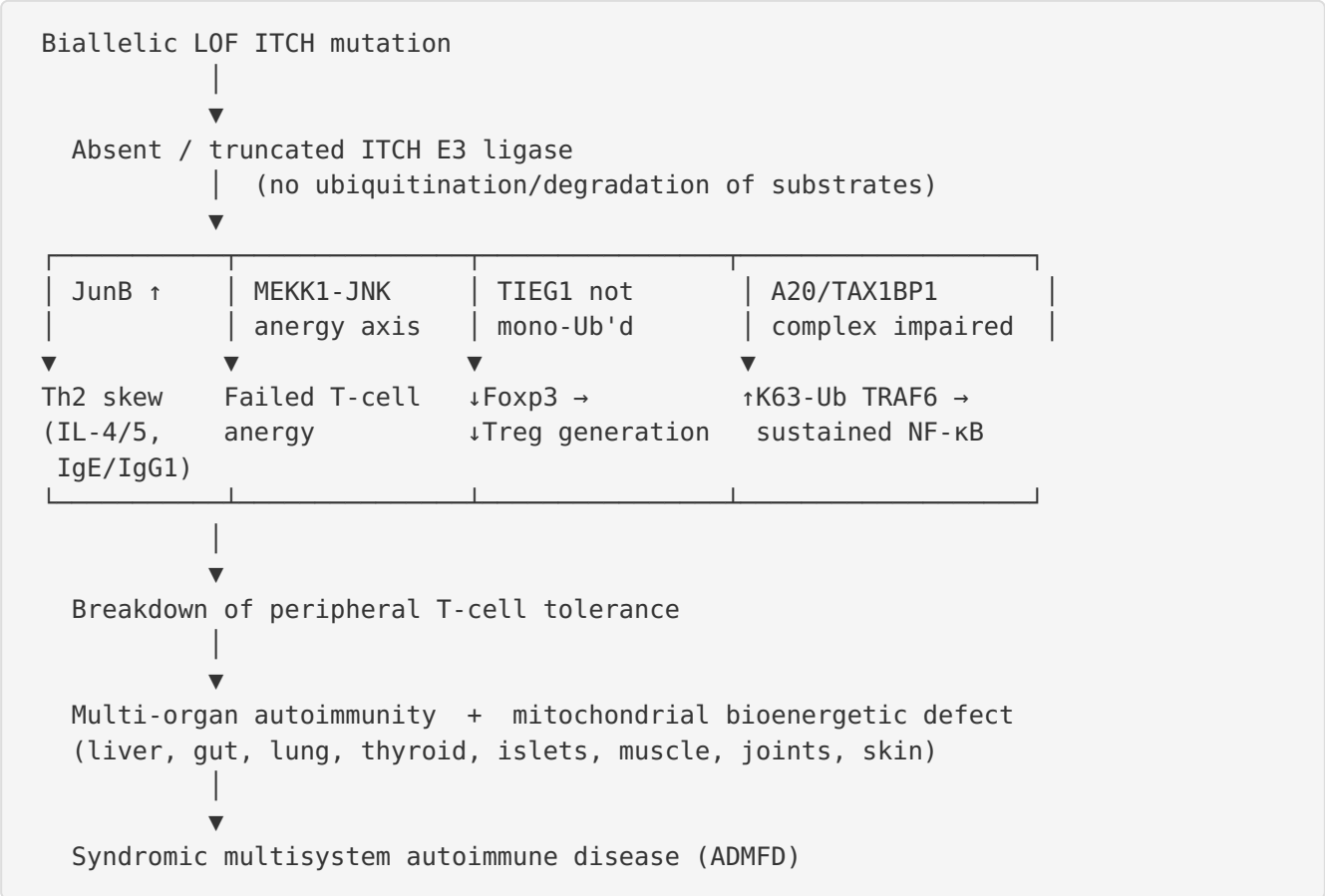
Protein dysfunction. Loss of function of the E3 ligase — the catalytic HECT domain (or the whole protein) is lost, abolishing substrate ubiquitination. ITCH *"is a HECT domain-containing E3 ligase that promotes the ubiquitylation and degradation of several proteins, including p73, p63, c-Jun, JunB, Notch and c-FLIP, thus affecting cell fate"* (PMID: 24787015).

Metabolic changes. Mitochondrial dysfunction: patient muscle mtDNA copy number was **57% of controls**, with decreased mitochondrial fatty-acid oxidation, decreased oxidative phosphorylation and decreased ATP production in fibroblasts (PMID: 36338154).

Immune system involvement. Central: autoimmunity driven by failed peripheral tolerance. *"E3 ligases Cbl-b and Itch have emerged as dominant 'tolerogenic' regulators of T cells because their deficiency results in severe autoimmune diseases"* (PMID: 20395198).

Cell types involved. CD4⁺ T helper cells (Th2), regulatory T cells (Foxp3⁺ Tregs), and antigen-stimulated effector T cells. Suggested **CL** terms: CL:0000624 (CD4-positive, alpha-beta T cell), CL:0000815 (regulatory T cell), CL:0000899 (Th2 cell).

Mechanistic schematic



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7. Anatomical Structures Affected

Organ level (primary). Liver (autoimmune hepatitis; UBERON:0002107), lung (chronic interstitial inflammation; UBERON:0002048), gastrointestinal tract / intestine (enteropathy; UBERON:0000160), thyroid gland (thyroiditis; UBERON:0002046), endocrine pancreas / islets (type 1 diabetes; UBERON:0000006), skeletal muscle (myositis; UBERON:0001134), joints (arthritis; UBERON:0001474), skin (psoriasis; UBERON:0002097), salivary/parotid gland (parotitis; UBERON:0001831).

Body systems. Immune/lymphoid (primary), hepatobiliary, respiratory, digestive, endocrine, musculoskeletal, integumentary.

Tissue and cell level. Autoimmune attack targets epithelial and glandular tissues (hepatocytes, intestinal and alveolar epithelium, thyroid follicular cells, pancreatic β-cells, salivary epithelium). Effector cells are lymphoid. In the mouse model there is **hyperplasia of lymphoid cells, haematopoietic cells and forestomach epithelium** (PMID: 9462742). Suggested CL terms: CL:0000624 ($CD4^+$ T cell), CL:0000815 (Treg), CL:0000899 (Th2 cell).

Subcellular level. Cytoplasm/plasma membrane (ITCH C2-domain membrane association; ubiquitination machinery), nucleus (transcription-factor substrates JunB/c-Jun/p63/p73/TIEG1→Foxp3), and **mitochondria** (bioenergetic defect). Suggested GO cellular-component terms: GO:0005829 (cytosol), GO:0005739 (mitochondrion), GO:0005634 (nucleus).

Localization / lateralization. Systemic and bilateral — a multi-organ, generalized autoimmune process without lateralization.

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8. Temporal Development

Onset. Early — neonatal to early childhood. The syndromic features (failure to thrive, facial dysmorphism, developmental delay) are congenital/early-infantile; autoimmune organ disease begins in infancy/childhood. Onset pattern is **insidious/chronic**.

Progression. Progressive and accumulating. Patients add autoimmune manifestations over time — a representative patient *"subsequently accumulated multiple autoimmune manifestations including autoimmune hepatitis, enteropathy, psoriasis, inflammatory arthritis, and Sjögren's-like parotitis"* (PMID: 42148098). Individual organ processes can be chronic-progressive (interstitial lung disease, hepatitis) or flaring. Progression rate is variable; overall course is chronic and lifelong absent curative therapy.

Patterns. Remission of individual manifestations is treatment-induced (immunosuppression) rather than spontaneous; the one reported **durable, multisystem remission** followed HSCT (PMID: 42148098). **Critical period / window of opportunity:** transplantation before irreversible end-organ damage (e.g., before fixed lung fibrosis or liver failure) is the key intervention window.

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9. Inheritance and Population

Inheritance. Autosomal recessive (OMIM #613385, MONDO:0013245). Disease requires two pathogenic *ITCH* alleles.

Epidemiology. Ultra-rare; no reliable prevalence/incidence figures. The original cohort comprised **10 consanguineous Old Order Amish patients**; subsequent individual patients of White British and Black German ethnicity have been reported, expanding the ethnic range beyond the Amish founder population (PMID: 36338154).

Penetrance / expressivity. Penetrance of the biallelic genotype appears high (essentially complete for the disorder), but **expressivity is variable** — which organs are affected and disease severity differ among patients, even within the founder genotype.

Founder effect / consanguinity. Strong founder effect in the Old Order Amish (single frameshift allele c.378_394del enriched by genetic isolation); consanguinity is a major risk circumstance, as expected for an AR disorder.

Carrier frequency. Elevated specifically within the Amish founder population; very low in the general population.

Demographics. No established sex predominance; affected individuals are children. Geographic clustering historically centered on Amish communities, with sporadic cases worldwide.

Genetic anticipation / mosaicism. Not applicable (not a repeat-expansion disorder); no germline-mosaicism reports.

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10. Diagnostics

Clinical laboratory. Organ-specific autoimmune serologies and function tests reflecting involved systems — e.g., elevated transaminases and autoantibodies / hypergammaglobulinemia in autoimmune hepatitis; thyroid autoantibodies; islet autoantibodies / hyperglycemia in T1D; muscle enzymes in myositis; blood counts (immune neutropenia). These are nonspecific individually.

Biomarkers. The definitive biomarker is molecular: biallelic pathogenic *ITCH* variants and/or **absent ITCH protein** on immunoblot of patient fibroblasts (PMID: 36338154). Mitochondrial studies (reduced mtDNA copy number; reduced fatty-acid oxidation / OXPHOS / ATP) can be a supportive cellular biomarker.

Imaging / functional / pathology. Chest imaging and pulmonary function for interstitial lung disease; liver biopsy may show interface hepatitis; muscle biopsy for myositis. Findings reflect the specific autoimmune organ disease rather than being disease-specific.

Genetic testing (the diagnostic cornerstone). Because the phenotype is syndromic and overlaps with other primary immune-regulatory and primary atopic disorders, **upfront broad genomic sequencing (WGS or WES)** is recommended for rapid diagnosis of such rare monogenic immune disorders (PMID: 39381601). Approaches in order of typical utility: WES/WGS → inborn-errors-of-immunity / primary-immunodeficiency gene panels including *ITCH* → targeted single-gene *ITCH* testing (useful in Amish probands where the founder allele is known). Chromosomal microarray/karyotype/FISH are not primary tools (no recurrent CNV cause in humans). mtDNA testing and repeat-expansion testing are not indicated.

Clinical criteria / differential diagnosis. No formal consensus diagnostic criteria exist; diagnosis is molecular. The differential includes other monogenic autoimmunity/immune-dysregulation syndromes — IPEX (FOXP3), CTLA-4 haploinsufficiency, LRBA deficiency, APECED (AIRE), STAT-related disorders, and primary atopic disorders (PMID: 39381601). Pediatric autoimmune hepatitis of unexplained cause should prompt consideration of *ITCH* mutation (PMID: 30705142), and atypical steroid-refractory cholestatic/hepatic disease warrants genetic testing (PMID: 41878599).

Screening. In the Amish, carrier/cascade screening for the known founder allele and prenatal/targeted testing are feasible. No general newborn screening exists.

11. Outcome / Prognosis

Survival / mortality. The disorder carries **high morbidity and mortality** without effective immune control. Autoimmune hepatitis can progress to **acute liver failure** (PMID: 30705142), and chronic interstitial lung disease can require tracheostomy and long-term ventilation (PMID: 42148098). The original Amish description emphasized severe multisystem disease. No formal 5-/10-year survival statistics exist for this ultra-rare condition.

Morbidity / function. Severe cumulative disability from progressive multi-organ autoimmunity, growth failure and developmental delay.

Disease course / complications. Complications include liver failure, respiratory failure, malabsorption/failure to thrive, endocrinopathy (T1D, thyroid disease), and complications of chronic immunosuppression (infection).

Recovery potential. With immunosuppression, individual manifestations can be controlled but not cured; relapse is typical. **Durable multisystem recovery has been achieved with HSCT** — sustained immune and pulmonary recovery three years post-transplant (PMID: 42148098).

Prognostic factors. Severity/number of organs involved, presence of irreversible end-organ damage (lung fibrosis, liver failure) at the time of definitive therapy, and access to HSCT.

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12. Treatment

Pharmacotherapy (immunosuppression/immunomodulation). Management is organ-directed immunosuppression — corticosteroids and steroid-sparing agents (e.g., azathioprine, mycophenolate, calcineurin inhibitors) for autoimmune hepatitis, enteropathy, myositis and arthritis; topical/systemic therapy for psoriasis; standard endocrine replacement for T1D and thyroid disease. Responses are partial and relapse is common. Suggested **NCIT** concepts: C15282 (Immunosuppressive Therapy), C305 (Corticosteroid), C2008 (Immunotherapy).

Advanced / curative therapeutics. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only reported disease-modifying/curative option: *"These findings support consideration of HSCT as a therapeutic option in carefully selected patients with severe, refractory autoimmune manifestations due to ITCH deficiency"* (PMID: 42148098), producing durable multisystem remission at three years. Suggested NCIT: C15431 (Hematopoietic Stem Cell Transplantation), C9306 (Allogeneic Bone Marrow Transplantation). Gene therapy, cell therapy (other than HSCT), RNA-based and targeted biologic therapies specific to ITCH deficiency are not yet established.

Pharmacogenomics. No ITCH-specific pharmacogenomic guidance. Of note, a drug-discovery screen identified antidepressants as modulators of ITCH activity/autophagy — a pharmacological-tool finding, not a therapy for this disease (PMID: 24787015).

Surgical / supportive / rehabilitative. Supportive care is central: nutritional support for failure to thrive/enteropathy, respiratory support (tracheostomy, ventilation), management of liver disease (including transplantation consideration for liver failure), and developmental/rehabilitative services.

Treatment strategy. Escalate from organ-directed immunosuppression to consideration of **HSCT in severe, refractory, multisystem disease**, ideally before irreversible end-organ damage. There are no published formal treatment algorithms or combination-therapy trials for ITCH deficiency specifically.

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13. Prevention

Primary prevention. Not possible for a monogenic recessive disease once both pathogenic alleles are inherited. Primary prevention is reproductive/genetic: **carrier screening, genetic counseling, and reproductive options** (prenatal diagnosis, preimplantation genetic testing), especially in the Amish founder population and consanguineous families.

Secondary prevention. Early molecular diagnosis via upfront genomic sequencing enables earlier immunomodulation and earlier consideration of HSCT — limiting cumulative organ damage (PMID: 39381601). Cascade testing of relatives of a proband (particularly for the known Amish allele) is valuable.

Tertiary prevention. Preventing complications in affected patients: vigilant surveillance for new autoimmune organ involvement, infection prophylaxis under immunosuppression, nutritional/respiratory support, and timely transplantation.

Counseling. Autosomal-recessive genetic counseling: 25% recurrence risk per pregnancy for carrier couples; cascade carrier testing; discussion of founder-allele frequency where relevant.

Immunization / public health / environmental. No disease-specific vaccine or public-health/environmental prevention; standard immunization caution applies under immunosuppression (avoid live vaccines as clinically indicated).

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14. Other Species / Natural Disease

Taxonomy / orthologs. Mouse ortholog *Itch* (MGI:1202301; NCBI Gene 16396; Ensembl ENSMUSG00000027598; chromosome 2). The gene and its tolerance function are evolutionarily conserved in mammals.

Natural disease in animals. The best-characterized natural/spontaneous model is the **mouse itchy mutant (non-agouti-lethal 18H, a18H)**, a spontaneously arising allele in which a paracentric inversion disrupts both *agouti* and *Itch* (PMID: 9462742). No companion-animal (OMIA-catalogued) natural ITCH-deficiency disease is established.

Comparative pathology. The mouse immunopathology strikingly parallels the human disease (multi-organ autoimmune/inflammatory involvement of lung, gut, skin and lymphoid tissue), supporting a conserved mechanism. **Zoonotic potential:** none (genetic disease).

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15. Model Organisms

Principal model — the itchy / a18H mouse. The *itchy* locus was discovered in non-agouti-lethal 18H (a18H) mice; *"a18H results from an inversion and ... Itch encodes a novel E3 ubiquitin protein ligase"* (PMID: 9462742). Affected mice develop **background-dependent immunopathology**: on some backgrounds inflammatory large-intestine disease; on C57BL/6J *"they develop a fatal disease characterized by pulmonary chronic interstitial inflammation and alveolar proteinosis, inflammation of the glandular stomach and skin resulting in scarring due to constant itching, and hyperplasia of lymphoid cells, haematopoietic cells and the forestomach epithelium"* (PMID: 9462742).

Mechanistic/knockout models. *Itch*$^{-/-}$ mice show Th2-skewed activation with elevated IL-4, IL-5, IgG1 and IgE, and defective Th2 tolerance: *"Itch associated with and induced ubiquitination of JunB, a transcription factor that is involved in TH2 differentiation"* (PMID: 11828324); and *"injection of high-dose tolerizing antigen failed to block the development of airway inflammation in Itch-/- mice"* (PMID: 16557301). These models also established the TIEG1→Foxp3/Treg and MEKK1-JNK axes.

Phenotype recapitulation. Excellent for the autoimmune/inflammatory (lung, gut, skin, lymphoid) and immunological (Th2 skew, failed tolerance, Treg deficit) features. **Limitations:** the mouse does not reproduce the human syndromic facial dysmorphism/developmental features, and the agouti-coat phenotype is a mouse-specific artifact of the linked inversion.

Cellular models: patient-derived skin fibroblasts have been used to show absent ITCH protein and the mitochondrial bioenergetic defect (PMID: 36338154). **Resources:** MGI (*Itch*, MGI:1202301).

Key Findings (with evidence)

F1 — Biallelic *ITCH* truncating mutation causes the disease (first human ITCH deficiency)

Autozygosity mapping in a large Old Order Amish kindred linked the disease to chromosome 20, identifying a homozygous truncating *ITCH* mutation in 10 affected patients; inheritance is autosomal recessive. *"Using autozygosity mapping in a large Amish kindred, we identified a linkage region on chromosome 20 and selected candidate genes for screening. We describe, in ten patients, identification of a mutation resulting in truncation of ITCH"* and these patients *"not only have multisystem autoimmune disease but also display morphologic and developmental abnormalities"* (PMID: 20170897).

F2 — ITCH is a HECT-domain E3 ligase with defined substrates

"ITCH is a HECT domain-containing E3 ligase that promotes the ubiquitylation and degradation of several proteins, including p73, p63, c-Jun, JunB, Notch and c-FLIP, thus affecting cell fate" (PMID: 24787015); *"Itch associated with and induced ubiquitination of JunB"* (PMID: 11828324).

F3 — ITCH enforces peripheral T-cell tolerance (Treg + anergy)

"Itch promotes ubiquitin conjugation to TGF-beta inducible early gene 1 product (TIEG1). Moreover, monoubiquitinated TIEG1 positively modulates the transcription of Foxp3 gene" (PMID: 19198068); *"injection of high-dose tolerizing antigen failed to block the development of airway inflammation in Itch-/- mice"* (PMID: 16557301); *"E3 ligases Cbl-b and Itch have emerged as dominant 'tolerogenic' regulators of T cells because their deficiency results in severe autoimmune diseases"* (PMID: 20395198).

F4 — Clinical spectrum and HSCT as disease-modifying therapy

"subsequently accumulated multiple autoimmune manifestations including autoimmune hepatitis, enteropathy, psoriasis, inflammatory arthritis, and Sjögren's-like parotitis" and *"These findings support consideration of HSCT as a therapeutic option in carefully selected patients with severe, refractory autoimmune manifestations due to ITCH deficiency"* (PMID: 42148098). ITCH mutation also causes pediatric intractable autoimmune hepatitis with risk of acute liver failure (PMID: 30705142).

F5 — ADMFD synonym and syndromic triad

"Autoimmune Disease, Multisystem, with Facial Dysmorphism (ADMFD) is an autosomal recessive disorder due to pathogenic variants in the ITCH gene. It is characterized by failure to thrive, dysmorphic facial features, developmental delay, and systemic autoimmunity..." and *"It was originally described in 10 consanguineous Old Order Amish patients, and more recently in two patients of White British and Black German ethnicities"* (PMID: 36338154).

F6 — Mitochondrial bioenergetic dysfunction (phenotype expansion)

"Clinical studies of patient muscle showed mitochondrial DNA copy number of 57% compared to controls. Functional studies in skin fibroblasts revealed decreased activity of mitochondrial fatty acid oxidation and oxidative phosphorylation, and decreased overall ATP production" (PMID: 36338154).

F7 — itchy/a18H mouse recapitulates the multi-organ disease

"they develop a fatal disease characterized by pulmonary chronic interstitial inflammation and alveolar proteinosis, inflammation of the glandular stomach and skin resulting in scarring due to constant itching, and hyperplasia of lymphoid cells, haematopoietic cells and the forestomach epithelium"; *"a18H results from an inversion and ... Itch encodes a novel E3 ubiquitin protein ligase"* (PMID: 9462742).

F8 — ITCH in the A20/TAX1BP1 complex restraining NF-κB

"...ubiquitin-editing enzyme A20 complex including A20, Tax1-binding protein 1 (TAX1BP1) and Itch, ... subsequently downregulated the K63-ubiquitination of TNF receptor associated factor 6 (TRAF6) and NF-κB signaling pathway" (PMID: 34454289).

F9 — Variant spectrum: biallelic LOF; Amish founder frameshift

RefSeq NM_031483.7; UniProt Q96J02 (903 aa); domains: C2 (aa 1–115), 4× WW (aa 326–511), HECT (aa 569–903). ClinVar P/LP alleles are overwhelmingly LOF (frameshift incl. founder c.378_394del; nonsense; canonical splice-site; start-loss). The founder allele yields a truncated protein (PMID: 20170897); other patients show complete absence of ITCH protein (PMID: 36338154).

F10 — Verified cross-reference identifiers

MONDO:0013245 ↔ OMIM 613385, Orphanet ORPHA:228426, GARD 0010775, MedGen/UMLS C3150649, NANDO 2200739, ICD-11 foundation 1970749000; gene ITCH HGNC:13890, NCBI 83737, Ensembl ENSG00000078747 (20q11.22); mouse Itch MGI:1202301, NCBI 16396.

Evidence Base

PMID	Title (abbrev.)	Evidence type	Supports
20170897	Human ITCH deficiency causes syndromic multisystem autoimmune disease	Human clinical / genetics	F1, F9 (gene discovery, founder allele, syndromic phenotype)
36338154	ITCH phenotype expansion & mitochondrial dysfunction	Human clinical / in vitro	F5, F6, F9 (ADMFD synonym, ethnic expansion, mitochondrial defect, absent protein)
42148098	Sustained recovery 3 yrs after HSCT for ITCH deficiency	Human clinical (case report)	F4 (clinical spectrum, curative HSCT)
30705142	ITCH mutation & pediatric autoimmune hepatitis / liver failure	Human clinical	F4, F5 (hepatic phenotype)
24787015	HTS for ITCH HECT ligase inhibitors	In vitro / biochemical	F2 (HECT class, substrate list, domains)
11828324	Itch in TH2 differentiation (itchy mice)	Model organism	F2, F3, F7 (JunB substrate, Th2 skew)
16557301	Itch ubiquitination + MEKK1-JNK in Th2 tolerance	Model organism	F3 (failed anergy, airway inflammation)
19198068	Itch regulates T-cell differentiation / Foxp3	Model organism / in vitro	F3 (TIEG1→Foxp3/Treg)
20395198	Cbl-b and Itch: peripheral T-cell tolerance	Review	F3 (tolerogenic role)
9462742	itchy locus / a18H mouse E3 ligase	Model organism	F7 (mouse model, inversion, E3 ligase)
34454289	A20 ubiquitin-editing complex (incl. Itch)	In vitro / mechanistic	F8 (A20/TAX1BP1-TRAF6-NF-κB)
39381601	Upfront genomic sequencing for primary atopic disorders	Review / methodology	Diagnostics (WGS/WES approach)
20108139	Foxp3⁺ Tregs regulated by Itch	Review	F3 (Treg regulation)

PMID	Title (abbrev.)	Evidence type	Supports
20143240	iTregs in T1D show higher ITCH levels	Human / in vitro	Context: ITCH–Treg–T1D link
41878599	Cholestatic liver disease / genetic testing in atypical cases	Human clinical	Diagnostics (genetic testing of atypical hepatic disease)
16493086	Itch/Cbl-b/Nedd4 anergy factors in filariasis	Human / mechanistic	Context: anergy-factor network

Limitations and Knowledge Gaps

- **Extreme rarity / small N.** Human evidence rests on a founder Amish cohort (n=10) plus scattered case reports. Prevalence, incidence, penetrance and sex ratio are not quantifiable; expressivity is clearly variable but poorly parameterized.
- **No natural-history or registry data.** Survival, long-term outcomes and QoL metrics are anecdotal.
- **Mechanistic attribution.** The NF-κB/A20 branch and the mitochondrial defect are demonstrated biochemically / in single patients, but their quantitative contribution to the human autoimmune phenotype is inferred, not proven. The link between mitochondrial dysfunction and autoimmunity is unresolved (parallel effect vs. causal contributor).
- **Model gaps.** The itchy mouse omits the human syndromic dysmorphism/developmental features, and strain background strongly modifies its phenotype — limiting direct translation.
- **Therapeutics.** HSCT evidence is a single durable-remission case; optimal timing, conditioning, patient selection and risk/benefit versus organ-directed immunosuppression remain undefined. No gene/RNA/targeted therapy exists.
- **Variant-level data.** Genotype–phenotype correlations across the (few) known alleles are not established.

Proposed Follow-up Experiments / Actions

1. **International patient registry & natural-history study** to quantify prevalence, organ-involvement frequencies, penetrance, survival and QoL, and to define genotype–phenotype correlations across known *ITCH* alleles.
2. **Systematic HSCT outcome collection** (timing, conditioning, GvHD, long-term immune/organ recovery) to build an evidence base for transplantation criteria and the therapeutic window before irreversible lung/liver damage.
3. **Deep immunophenotyping of patients** (Treg number/function, Th2 cytokines, NF-κB activation signatures) to validate, in humans, the Treg/anergy/NF-κB branches established in mice, and to identify monitorable biomarkers.
4. **Mechanistic dissection of the mitochondrial phenotype** — determine whether ITCH loss directly perturbs mitochondrial substrates/bioenergetics or whether the defect is secondary to chronic inflammation; test whether it contributes to tissue damage.
5. **Preclinical targeted-therapy evaluation** in *Itch*$^{-/-}$ mice — e.g., JAK/NF-κB inhibitors, Th2-directed biologics (anti-IL-4/IL-5), or Treg-enhancing strategies (low-dose IL-2) — to find disease-modifying pharmacotherapy short of HSCT.
6. **Patient-derived iPSC/organoid and gene-correction models** to study tissue-specific pathology and to provide a platform for future gene-replacement/editing approaches.
7. **Carrier/cascade screening programs** for the Amish founder allele with integrated genetic counseling and reproductive options.

Report compiled from 10 confirmed findings and 16 reviewed papers over a 5-iteration autonomous investigation. Causal gene confirmed as ITCH (HGNC:13890) per the provided MONDO:0013245 / OMIM 613385 identifiers.
