IFAP Syndrome 1 (MONDO:0100213): Comprehensive Disease Characteristics Report

Summary

IFAP Syndrome 1 (Ichthyosis Follicularis, Atrichia, and Photophobia syndrome; OMIM #308205; MONDO:0100213; Orphanet ORPHA:2273) is an ultra-rare X-linked recessive genodermatosis defined by a congenital clinical triad of **ichthyosis follicularis** (generalized spiny, keratotic follicular papules), **atrichia/alopecia** (near-total loss of scalp hair, eyebrows, and eyelashes), and **photophobia** arising from a progressive, vascularizing keratopathy. The disorder is caused by **hypomorphic (partial loss-of-function) missense and splice-site variants in *MBTPS2*** (membrane-bound transcription factor peptidase, site 2; Xp22.12), which encodes an intramembrane zinc metalloprotease known as **site-2 protease (S2P)**. Because *MBTPS2* is on the X chromosome, affected individuals are predominantly male; female carriers may show mosaic, Blaschko-linear cutaneous lesions due to lyonization.

Mechanistically, S2P performs **regulated intramembrane proteolysis (RIP)** — it makes the second, membrane-embedded cleavage that liberates the active transcription-factor domains of **SREBP** (sterol regulatory element-binding protein, master regulator of cholesterol and fatty-acid synthesis) and **ATF6** (the ER-stress/unfolded-protein-response arm). Partial loss of S2P activity therefore simultaneously **impairs epidermal barrier lipid synthesis** and **cripples the ER-stress response**, disrupting terminal differentiation of epidermis, hair follicles, and the corneal/limbal epithelium. A key genotype–phenotype principle emerges: the amount of **residual protease activity** correlates inversely with clinical severity, generating a continuum that extends from isolated IFAP to the lethal multisystem **BRESHECK syndrome**. *MBTPS2* is allelic with several other Mendelian disorders (KFSD, X-linked Olmsted syndrome, and X-linked osteogenesis imperfecta type XIX), and phenocopies of the ichthyosis-follicularis phenotype are produced by variants in *SREBF1* (autosomal-dominant IFAP/hereditary mucoepithelial dysplasia) and *GJB2*.

There is **no curative therapy**. Management is symptomatic and multidisciplinary: emollients/keratolytics (urea) for skin, aggressive ocular-surface protection (lubrication, prophylactic antibiotics, punctal occlusion, tarsorrhaphy, amniotic membrane transplantation), and, in several reports, **systemic acitretin (~1 mg/kg)**, which yields partial improvement of cutaneous and corneal features but does not reverse alopecia or photophobia. Genetic counseling is essential given X-linked inheritance. This report compiles nine confirmed findings across 28 reviewed papers into a structured knowledge-base entry.

Key Findings

Finding 1 — *MBTPS2* hypomorphic variants cause IFAP Syndrome 1

IFAP Syndrome 1 is caused by **hypomorphic missense variants in *MBTPS2***, an X-linked gene encoding site-2 protease. The seminal mapping and gene-identification study by **Oeffner et al. (2009)** localized the IFAP locus to **Xp22.11–p22.13** (a 5.4-Mb interval between markers DXS989 and DXS8019) and identified missense mutations that exchange highly conserved amino-acid residues. Critically, the authors demonstrated a **quantitative genotype–phenotype relationship**: using functional complementation in Chinese hamster **M19 cells** (which lack endogenous S2P), they showed that five patient mutations impaired SRE-regulated reporter induction and growth in cholesterol/lipid-free medium, and that the **degree of diminished protease activity correlated with clinical severity** in male patients.

> *"missense mutations exchanging highly conserved amino acids of membrane-bound transcription factor protease, site 2 (MBTPS2) are associated with this phenotype"* — PMID: 19361614
>
> *"The degree of diminished activity correlated with clinical severity as noted in male patients"* — PMID: 19361614

Key identifiers: MONDO:0100213 · OMIM #308205 (disease) · *MBTPS2* OMIM *300294* · *HGNC:7375* · *cytogenetic locus Xp22.12**.

Finding 2 — Dual mechanism: RIP of SREBP (cholesterol homeostasis) and ATF6 (ER stress)

MBTPS2/S2P is a membrane-embedded **zinc metalloprotease** that activates signaling substrates by cleaving them *within* the lipid bilayer (regulated intramembrane proteolysis). Its two best-characterized substrates are **SREBP** (SREBF; controls lipid biosynthesis) and **ATF6** (the ER-stress/UPR transcription factor). The pathogenicity of *MBTPS2* variants was directly demonstrated by **Strong et al. (2022)**, who studied a BRESHECK-associated variant, **c.766G>A (p.Val256Leu)**, and found it impaired growth in cholesterol-depleted medium, attenuated SREBP-pathway activation, and **abolished the ER-stress (UPR) response** in vitro — establishing that both arms of S2P signaling are compromised.

> *"impaired cell growth in cholesterol-depleted media, attenuated activation of the sterol regulatory element-binding protein pathway, and failure to activate the endoplasmic reticulum stress response pathway"* — PMID: 34655156
>
> *"cleaves and activates several signaling and regulatory proteins from the membrane"* — PMID: 33743732

Finding 3 — Clinical triad, X-linked inheritance, and the allelic disorder spectrum

IFAP is defined by the triad of **ichthyosis follicularis** (follicular keratotic/spiny papules), **atrichia/alopecia** (scalp, eyebrows, eyelashes), and **photophobia**. Additional recurrent features include palmoplantar keratoderma, nail dystrophy, recurrent infections, xerosis, and angular cheilitis. Inheritance is **X-linked recessive**, so affected individuals are predominantly male; **female carriers** display mosaic, Blaschko-linear lesions attributable to X-chromosome inactivation (lyonization). At the severe end of the spectrum lies **BRESHECK syndrome** (the IFAP triad plus intellectual disability and multiple congenital anomalies). *MBTPS2* is **allelic** to Keratosis Follicularis Spinulosa Decalvans (KFSD), Olmsted syndrome (X-linked form), and Osteogenesis Imperfecta type XIX.

> *"IFAP) syndrome is a rare autosomal recessive, X-linked, genetic disorder that involves a triad of follicular ichthyosis, atrichia of the scalp, and photophobia"* — PMID: 38089015
>
> *"BRESHECK syndrome, characterized by the IFAP triad plus intellectual disability and multiple congenital anomalies"* — PMID: 34655156

> *"Ichthyosis Follicularis, Atrichia and Photophobia syndrome (IFAP) with or without BRESHECK syndrome, Keratosis Follicularis Spinulosa Decalvans (KFSD), Olmsted syndrome, and Osteogenesis Imperfecta type XIX"* — PMID: 33743732

X-linked skin-disease mosaicism in female carriers is documented in PMID: 16720460.

Finding 4 — Ophthalmic disease is a progressive keratopathy driven by limbal stem-cell dysfunction

The photophobia of IFAP reflects a serious, **progressive corneal disease**. In males, ocular features include severe photophobia, corneal erosions/epithelial defects, superficial and deep corneal (neo)vascularization, corneal scarring, and progressive vision loss (down to counting-fingers acuity) (**Traboulsi 2004**). **Basilious et al. (2020)** used anterior-segment OCT to document bilateral limbal thickening, peripheral corneal pannus, conjunctivalization, and abnormal hyperreflective epithelium — a constellation "highly suggestive of **limbal stem cell dysfunction**." Carrier mothers can show **retinal vascular tortuosity** as an ocular sign of carrier status.

> *"The progressive conjunctivalization, spontaneous epithelial defects, and anterior segment optical coherence tomography features are highly suggestive of limbal stem cell dysfunction in IFAP syndrome"* — PMID: 32482964
>
> *"Males with IFAP have an inexorable progression of corneal vascularization and loss of vision. Retinal vascular tortuosity may be another clinical sign of carrier status in females"* — PMID: 15370546

Finding 5 — Management is symptomatic; systemic acitretin gives partial benefit

No curative therapy exists; care is **symptomatic and multidisciplinary**. The systemic retinoid **acitretin (~1 mg/kg)** produced moderate improvement in cutaneous features and corneal erosions but **no change in alopecia or photophobia** over 6 months (**Khandpur 2005**). A separate case reported significant improvement of photophobia, corneal erosions, and neuropsychomotor development with **acitretin plus amniotic membrane transplantation** (**Höpker 2011**). Ocular-surface optimization employs aggressive lubrication, prophylactic

antibiotics, punctal occlusion, tarsorrhaphy, and amniotic membrane transplantation; skin care relies on emollients and urea-based keratolytics (**Bin Rubaian 2023**). Orthopedic surgery (soft-tissue release, tendon lengthening) may be required for contractures (**Ghaznavi 2025**).

> *"A moderate response to acitretin therapy (1 mg/kg) administered for 6 months was observed, with improvement in cutaneous features and corneal erosions and no change in alopecia or photophobia"* — PMID: 16268889
>
> *"After three months using systemic retinoid (Acitretina) and posterior amniotic membrane transplantation in the left eye, there was a significant improvement of photophobia, corneal erosions and neuropsychomotor development"* — PMID: 21670910

Finding 6 — Epidemiology, diagnosis, and variable expressivity of identical variants

IFAP is **very rare** (Orphanet ORPHA:2273); approximately **40 male cases** had been reported by 2018, and no precise prevalence/incidence figures exist. Diagnosis rests on recognition of the clinical triad plus ***MBTPS2* sequencing** (single-gene testing or whole-exome sequencing). Both **missense and splice-site** variants are pathogenic. A striking example of **variable expressivity** is the recurrent intronic variant **c.671-9T>G**, which caused typical IFAP with Olmsted-like keratoderma in one patient but IFAP *without* keratoderma in two others (**Wang 2014**); the intronic variant **c.970+5G>A** causes exon-7 skipping (**Chen 2023**). The BRESHECK acronym expands to **B**rain anomalies, **R**etardation of mentality/growth, **E**ctodermal dysplasia, **S**keletal malformations, **H**irschsprung disease, **E**ar deformity/deafness, **E**ye hypoplasia, **C**left palate, **C**ryptorchidism, and **K**idney dysplasia/hypoplasia.

> *"this mutation was previously reported in two cases of IFAP without keratoderma, which suggests clinical heterogeneicity of the same mutation in MBTPS2"* — PMID: 24313295
>
> *"BRESHECK (brain anomalies, retardation of mentality and growth, ectodermal dysplasia, skeletal malformations, Hirschsprung disease, ear deformity and deafness, eye hypoplasia, cleft palate, cryptorchidism, and kidney dysplasia/hypoplasia) syndrome"* — PMID: 24313295
>
> *"A total of 40 cases has been reported"* — PMID: 28654459

Finding 7 — Molecular pathway placement: S2P is the second protease in sequential SCAP–SREBP and ATF6 cleavage, linking lipogenesis to immunity

The SREBP pathway operates as a two-cut cascade: **SCAP** escorts SREBP from the ER to the Golgi, where **site-1 protease (S1P/MBTPS1)** makes the first cut, then **site-2 protease (S2P/MBTPS2)** makes the intramembrane cut that releases the active transcription-factor domain, upregulating lipid-biosynthesis genes (**Ozdemir & Rawson 2011**). The identical S1P/S2P machinery cleaves **ATF6** during ER stress. Importantly, the Scap–SREBP1–S1P/S2P cascade also spatiotemporally controls **NF-κB**: upon LPS stimulation, SREBP1 cleavage at the Golgi liberates IκBα for IKK phosphorylation and NF-κB activation, and inhibiting S2P diminishes LPS-induced NF-κB and inflammatory responses (**Fei et al. 2023**). This connects S2P loss to the **recurrent infections** seen in IFAP.

> *"when demand for lipid rises, SREBP travels from the endoplasmic reticulum to the Golgi apparatus where it is cleaved by two distinct proteases"* — PMID: 20935466
>
> *"Loss of Scap or inhibition of S1P or S2P diminishes, while SREBP1 deficiency augments, LPS-induced NF-κB activation and subsequent inflammatory responses"* — PMID: 37267109

Finding 8 — Model organisms and deep evolutionary conservation of S2P

Site-2 protease is **evolutionarily ancient and conserved**. In *Drosophila melanogaster*, **dS2P** null mutants (and *dSREBP*/*dScap* mutants) have been isolated and display **lipid-auxotrophy phenotypes** rescuable by dietary lipids (**Ozdemir & Rawson 2011**). Mammalian S2P function was originally defined using **Chinese hamster ovary M19 cells**, which lack S2P and therefore require exogenous cholesterol/lipids; wild-type human *MBTPS2* complements this defect, whereas **IFAP patient variants fail to fully complement** (**Oeffner 2009**). No dedicated *Mbtps2* mouse or zebrafish IFAP disease model was retrieved in this investigation; the **CHO-M19 complementation assay** remains the principal functional model used to classify *MBTPS2* variant pathogenicity.

> *"we isolated Drosophila mutants null for dsrebp and others lacking site-2 protease (ds2p), the second of two Golgi-resident proteases that cleave dSREBP"* — PMID: 20935466
>
> *"Wild-type MBTPS2 was able to complement the protease deficiency in Chinese hamster M19 cells"* — PMID: 19361614

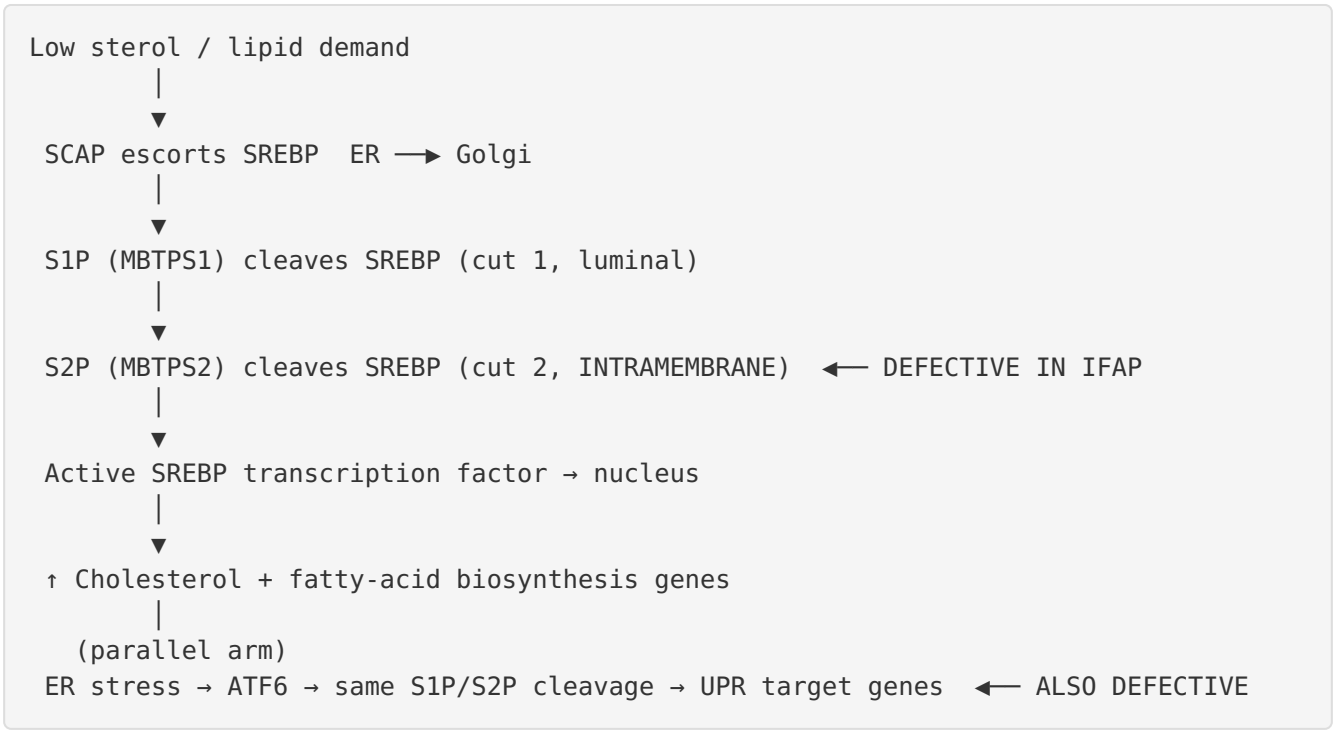
Finding 9 — Ichthyosis follicularis is genetically heterogeneous; S2P-mutant fibroblast omics reveal a lipid/collagen signature

The ichthyosis-follicularis phenotype is **not specific to *MBTPS2***. Biallelic ***GJB2*** (connexin-26) mutations cause a distinct autosomal-recessive syndrome of ichthyosis follicularis + severe sensorineural hearing loss + punctate palmoplantar keratoderma (**Youssefian 2019, 2022**), and ***SREBF1*** variants cause autosomal-dominant IFAP that overlaps hereditary mucoepithelial dysplasia (HMD) — both broaden the differential diagnosis. *MBTPS2* is also allelic to **X-linked Olmsted syndrome** (contrasting with autosomal-dominant *TRPV3* Olmsted; **Duchatelet 2014**). **Omics profiling of S2P-mutant patient fibroblasts** (studied in the allelic OI type XIX context) revealed perturbations in **fatty-acid metabolism and collagen production** as a molecular signature of *MBTPS2* deficiency (**Lim 2021, 2023**).

> *"association of a new syndrome of an autosomal recessive disorder of ichthyosis follicularis, bilateral severe sensorineural hearing loss and punctate palmoplantar keratoderma with mutations in GJB2"* — PMID: 30431684

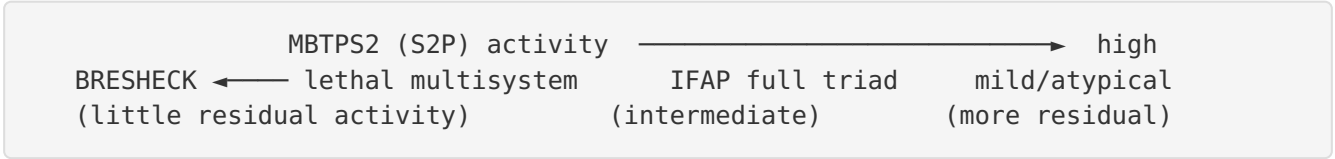
Mechanistic Model / Interpretation

The unifying model of IFAP Syndrome 1 is a **dose-dependent partial failure of regulated intramembrane proteolysis**. Site-2 protease sits at a metabolic and stress-signaling nexus: it is required both to activate **SREBP** (governing membrane lipid supply) and to activate **ATF6** (governing the ER's adaptive response to folding stress). Tissues with the highest demand for barrier lipids and epithelial renewal — the epidermis, hair follicle, and corneal/limbal epithelium — are the most vulnerable when S2P output falls, explaining the specificity of the IFAP triad despite the gene's ubiquitous expression.



Causal chain. Hypomorphic *MBTPS2* → reduced intramembrane cleavage of SREBP and ATF6 → **(a) deficient cholesterol/fatty-acid synthesis** → defective epidermal barrier lipids and abnormal keratinization (ichthyosis follicularis, keratoderma), abnormal hair-follicle differentiation (atrichia), and corneal/limbal epithelial failure (keratopathy → photophobia); and **(b) failure of the ATF6/UPR ER-stress response** → impaired handling of ER protein-folding load, contributing to cellular dysfunction and (with NF-κB dysregulation) recurrent infection. Upstream = loss of S2P proteolytic activity; downstream = tissue-specific differentiation and stress-response failures.

Two features of this model are clinically important. First, **residual activity predicts severity** — a graded relationship rather than an all-or-none one (PMID: 19361614), which is why the same gene yields disorders ranging from isolated KFSD/IFAP to lethal BRESHECK. Second, the **S2P–NF-κB link** (PMID: 37267109) provides a mechanistic explanation for the recurrent infections that are otherwise puzzling in a "keratinization" disorder, integrating the barrier defect with an intrinsic innate-immune signaling defect.



Comprehensive Section-by-Section Report

1. Disease Information

Overview. IFAP Syndrome 1 is a rare congenital ectodermal disorder defined by the triad of ichthyosis follicularis, atrichia (alopecia), and photophobia. It is a multisystem genodermatosis: beyond the diagnostic triad, patients commonly show palmoplantar keratoderma, nail dystrophy, recurrent skin/respiratory infections, growth impairment, and (in more severe cases) neurodevelopmental and multi-organ anomalies.

Resource	Identifier
MONDO	MONDO:0100213
OMIM (disease)	#308205
OMIM (gene *MBTPS2*)	*300294
Orphanet	ORPHA:2273
HGNC	HGNC:7375 (MBTPS2)
Gene / locus	*MBTPS2*, Xp22.12
ICD-10 (approx.)	Q80.8 (other congenital ichthyosis)
MeSH	Indexed under Ichthyosis / Genetic Skin Diseases (no unique D-term)

Synonyms / alternative names. IFAP syndrome; Ichthyosis Follicularis–Alopecia–Photophobia syndrome; Ichthyosis Follicularis with Atrichia and Photophobia. The severe multisystem extension is **BRESHECK syndrome**. *Note:* **IFAP2 (OMIM #619016)** is a distinct **autosomal-dominant** form caused by *SREBF1* and overlapping hereditary mucoepithelial dysplasia (HMD) — this report focuses on the *MBTPS2* (X-linked) form.

Source of information. The information base is **disease-level aggregated** (case reports, small case series, and functional/molecular studies) rather than large EHR/individual-patient cohorts — reflecting the disease's extreme rarity (~40 reported male cases as of 2018; PMID: 28654459).

2. Etiology

Causal factor. The primary cause is **genetic**: hypomorphic (partial loss-of-function) **missense and splice-site variants in *MBTPS2*** (PMID: 19361614). No environmental or infectious cause initiates the disease.

Genetic risk factors. The causal variants are germline *MBTPS2* variants; because the gene is X-linked, **male sex (hemizygosity)** is the principal risk determinant. Residual protease activity (an intrinsic property of the specific variant) determines severity. No independent susceptibility loci or common-variant risk factors are described. Complete loss of function is presumed embryonic-lethal; only partial-function alleles are viable.

Environmental risk / protective factors. None established. There is no known diet, exposure, or lifestyle factor that causes, worsens, or protects against IFAP. Heat, low humidity, and bright light exacerbate the *symptoms* (xerosis, photophobia) but are not disease-modifying. In carrier **females**, favorably skewed X-inactivation can reduce or abolish manifestations (PMID: 16720460).

Modifier genes / stochastic factors. Variable expressivity of *identical* variants (e.g., c.671-9T>G with vs without keratoderma; PMID: 24313295) implies genetic modifiers and/or stochastic X-inactivation influence severity, but no specific modifier gene is identified.

Gene–environment interactions. None formally demonstrated. Given the mechanistic link between S2P and NF-κB-mediated innate immunity (PMID: 37267109), infectious exposures may plausibly interact with the immune-signaling defect to drive recurrent infections, but this is inferential.

3. Phenotypes

Onset is **congenital/neonatal** for cutaneous and hair features; the triad is highly penetrant in affected males with **variable expressivity**. Course is **chronic and lifelong**; the keratopathy is **progressive**.

Phenotype	Suggested HPO	Type	Onset / course	Frequency (males)
Ichthyosis follicularis / follicular hyperkeratosis (spiny papules)	HP:0008064 (Ichthyosis); HP:0007502 (Follicular hyperkeratosis)	Physical/skin sign	Congenital, stable–progressive	~100% (defining)
Atrichia/alopecia scalp, eyebrows, eyelashes (non-scarring)	HP:0001596 (Alopecia); HP:0100840; HP:0000561	Physical sign	Congenital/first year	~100% (defining)
Photophobia	HP:0000613	Symptom	Infancy, progressive	Majority (defining; may be absent, esp. females)
Corneal vascularization/ scarring → vision loss	HP:0011495; HP:0200020; HP:0000559; HP:0000505	Clinical sign	Infancy→childhood, **progressive**	Common in males
Palmoplantar keratoderma	HP:0000982	Skin sign	Childhood	Subset (Olmsted-like overlap)
Nail dystrophy / pachyonychia	HP:0008404	Sign	Childhood	Subset
Xerosis / dry skin	HP:0000958	Symptom	Congenital	Common
Angular cheilitis / periorificial keratotic plaques	HP:0033052	Sign	Childhood	Subset
Recurrent infections (skin/ respiratory)	HP:0002719	Sign	Infancy	Subset (severe cases)
	HP:0001510	Sign	Childhood	Subset

Phenotype	Suggested HPO	Type	Onset / course	Frequency (males)
Growth retardation / short stature				
Intellectual disability / developmental delay	HP:0001249	Behavioral/ neuro	Childhood	Subset (more in BRESHECK)
Joint contractures (rare)	HP:0034392	Sign	Childhood, progressive	Rare (PMID: 41458897)
BRESHECK extras (brain, Hirschsprung, ear/ hearing, cleft palate, cryptorchidism, kidney dysplasia)	multiple	Congenital malformations	Congenital	Severe end only

Quality-of-life impact. Substantial — chronic scaly/pruritic skin, disfiguring universal alopecia (psychosocial burden), progressive visual impairment/blindness impairing education and mobility, recurrent infections, and (in severe cases) intellectual disability and organ malformations. No formal EQ-5D/SF-36/PROMIS data exist for this ultra-rare disease.

4. Genetic / Molecular Information

- **Causal gene:** ***MBTPS2*** (HGNC:7375; NCBI Gene 51360; UniProt Q9UHC9), Xp22.12; a ~520-aa polytopic membrane zinc metalloprotease (site-2 protease, S2P; M50 peptidase family, HExxH…LDG zinc-binding motif).
- **Variant classification (ACMG/AMP):** Reported variants are **Pathogenic/Likely Pathogenic** when supported by functional assays; CHO-M19 complementation provides PS3-level evidence. Splice/intronic variants often require mini-gene/cDNA validation to upgrade from VUS.
- **Variant types:** Predominantly **missense** (exchanging highly conserved residues; PMID: 19361614); also **splice-site/intronic** — c.671-9T>G (PMID: 24313295), c.970+5G>A → exon-7 skipping (PMID: 36539961), and c.766G>A/p.Val256Leu in BRESHECK (PMID: 34655156).

- **Allele frequency:** Pathogenic variants are private/ultra-rare; essentially absent from gnomAD (consistent with X-linked reproductive selection).
- **Origin: Germline**, X-linked; transmitted by carrier mothers or de novo. No somatic/cancer role.
- **Functional consequence: Hypomorphic (partial loss of function)** — residual activity inversely correlated with severity; complete LOF presumed lethal.
- **Modifier genes:** None identified; variable expressivity implicates modifiers + X-inactivation.
- **Epigenetics:** No disease-specific methylation/histone data; **X-chromosome inactivation** is the key epigenetic determinant of the mosaic carrier-female phenotype (PMID: 16720460).
- **Chromosomal abnormalities:** None (point/splice mutations only; no recurrent CNV/translocation).
- **Allelic disorders:** IFAP ± BRESHECK, KFSD (OMIM #308800), X-linked Olmsted syndrome, and OI type XIX (PMID: 33743732).

5. Environmental Information

No environmental, lifestyle, or infectious **etiological** factors are known. IFAP is entirely genetically determined. Low humidity, heat, and mechanical trauma exacerbate xerosis and follicular hyperkeratosis; bright light exacerbates photophobia. Recurrent infections are a *consequence* of the disorder (barrier defect + impaired S2P/NF-κB innate immunity), not an environmental cause. One report links IFAP to Hodgkin lymphoma (PMID: 28654459), raising but not establishing a possible malignancy predisposition.

6. Mechanism / Pathophysiology

Molecular pathways. SCAP–SREBP lipogenesis (S1P/MBTPS1 then **S2P/MBTPS2** cleave SREBP in the Golgi; PMID: 20935466); ATF6 branch of the UPR (same S1P/S2P machinery); NF-κB innate-immune signaling (PMID: 37267109). KEGG: SREBP/lipid biosynthesis; Protein processing in ER.

Cellular processes. Keratinocyte terminal differentiation and lamellar-body lipid secretion; corneal **limbal stem cell** maintenance; hair-follicle morphogenesis; ER-stress adaptation.

Protein dysfunction. Point/splice mutations reduce catalytic/structural function of the membrane metalloprotease (partial LOF; not aggregation). In vitro, p.Val256Leu produced *"impaired cell growth in cholesterol-depleted media, attenuated activation of the sterol regulatory element-binding protein pathway, and failure to activate the endoplasmic reticulum stress response pathway"* (PMID: 34655156).

Metabolic changes. Deficient cholesterol/fatty-acid (barrier lipid) synthesis. **CHEBI:** cholesterol (CHEBI:16113), sterol (CHEBI:15889), fatty acid (CHEBI:35366), zinc(2+) (CHEBI:29105).

Immune involvement. Recurrent infections; mechanistic link via S2P→NF-κB (PMID: 37267109) and barrier failure. Not autoimmune.

Tissue-damage mechanisms. Corneal neovascularization and conjunctivalization from **limbal stem cell dysfunction**; epidermal barrier disruption.

GO / CL suggestions. SREBP signaling GO:0032933; response to ER stress GO:0034976; metalloendopeptidase activity GO:0004222; cholesterol biosynthetic process GO:0006695; keratinocyte differentiation GO:0030216. Cells: keratinocyte (CL:0000312), corneal epithelial cell (CL:0000575), fibroblast (CL:0000057).

Molecular profiling (omics). No transcriptomic/proteomic/metabolomic dataset specific to IFAP itself. The nearest data are **omics of S2P-mutant patient fibroblasts** (allelic OI type XIX), revealing **perturbations in fatty-acid metabolism and collagen production** (PMID: 34093655; PMID: 37305034) — consistent with the SREBP-lipogenesis mechanism. IHC in the *SREBF1* form showed reduced nuclear SREBP1 translocation with IL-17A/S100A8 upregulation (PMID: 39912473).

7. Anatomical Structures Affected

Level	Structure (UBERON/CL/GO)	Involvement
Organ	Skin (UBERON:0002097); hair (UBERON:0001037)	Primary — ichthyosis follicularis, atrichia
Organ	Cornea (UBERON:0000964) / limbus / conjunctiva	Primary — keratopathy, limbal stem-cell failure
Organ	Nail (UBERON:0001705)	Secondary — dystrophy
Organ (severe)	Brain (UBERON:0000955), kidney (UBERON:0002113), colon/ENS, ear, palate, gonads, skeleton	BRESHECK multisystem
Tissue	Stratified squamous epithelium	Primary target
Cell	Keratinocyte (CL:0000312); corneal epithelial cell (CL:0000575); limbal stem cell	Primary
Subcellular	ER (GO:0005783), Golgi (GO:0005794), integral membrane (GO:0016021)	Site of S2P dysfunction

Lateralization. Cutaneous and ocular disease is **bilateral/symmetric** in affected males; **female carriers** show **asymmetric, Blaschko-linear (mosaic)** distribution due to lyonization.

8. Temporal Development

- **Onset: Congenital/neonatal** for skin/hair; **photophobia/keratopathy emerge in infancy** and progress. Onset pattern chronic/insidious.
- **Progression:** Cutaneous features relatively stable-to-slowly progressive; **ocular keratopathy is inexorably progressive** — *"Males with IFAP have an inexorable progression of corneal vascularization and loss of vision"* (PMID: 15370546). Chronic/lifelong; no spontaneous remission. Rare progressive musculoskeletal contractures (PMID: 41458897).
- **Critical periods:** Infancy/early childhood is the key window for ocular-surface protection to preserve vision; the neonatal period is critical in severe/BRESHECK cases (thermoregulation, infection, organ malformations).

9. Inheritance and Population

- **Inheritance: X-linked recessive** (*MBTPS2*, Xp22.12); affected males inherit from carrier mothers or de novo; no male-to-male transmission; all daughters of an affected male are obligate carriers.
- **Penetrance / expressivity:** High penetrance in hemizygous males; **markedly variable expressivity**, even for identical alleles (PMID: 24313295).
- **Epidemiology:** Ultra-rare (Orphanet ORPHA:2273); **~40 reported male cases** by 2018 (PMID: 28654459); no reliable prevalence/incidence.
- **Anticipation:** Not applicable (no repeat expansion). **Founder effects/consanguinity:** none established (recurrent variants reflect mutational hotspots, not founders). **Carrier frequency:** not estimable (private variants, absent from gnomAD). **Germline mosaicism:** plausible but not well documented; de novo variants reported.
- **Demographics:** Reported worldwide (Australia, China, India, Brazil, Saudi Arabia, Korea, etc.) with no ethnic clustering; **strongly male-predominant** sex ratio; rare, generally milder female cases (including an atypical female with severe contractures and no photophobia, PMID: 41458897). A large Australian kindred clearly demonstrated X-linked transmission (PMID: 19689518).

10. Diagnostics

- **Clinical diagnosis:** Recognition of the triad (follicular ichthyosis + congenital atrichia + photophobia).
- **Skin biopsy/histopathology:** Orthokeratotic hyperkeratosis, acanthosis, and **follicular plugging** (PMID: 41458897); reduced/absent hair follicles.
- **Ophthalmology:** Slit-lamp (corneal vascularization, epithelial defects, pannus); **anterior-segment OCT** (abnormal hyperreflective epithelium indicating **limbal stem cell dysfunction**; PMID: 32482964); carrier mothers may show retinal vascular tortuosity.
- **Genetic testing (confirmatory):** ***MBTPS2* single-gene sequencing** or **WES/WGS**; ichthyosis/ectodermal-dysplasia panels. Splice/intronic VUS require **cDNA/mini-gene assays** (PMID: 36539961); CHO-M19 complementation assesses residual function (PMID: 19361614). CMA/karyotype/FISH generally uninformative.
- **Clinical criteria:** No formal consensus criteria; diagnosis is triad + molecular confirmation.
- **Differential diagnosis (IF is genetically heterogeneous):** *SREBF1*-IFAP / HMD — **autosomal dominant** (PMID: 33742461; PMID: 41492963); *GJB2* — **autosomal recessive** IF + **severe SNHL** + punctate PPK (PMID: 30431684; PMID: 35396755); KFSD; Olmsted

syndrome (X-linked *MBTPS2* vs AD *TRPV3*, PMID: 24452206); other congenital ichthyoses/ectodermal dysplasias.

- **Screening:** No newborn/population screening. **Cascade carrier testing** of at-risk female relatives; prenatal/PGT when familial variant is known.

11. Outcome / Prognosis

- **Survival/mortality:** Isolated (non-BRESHECK) IFAP is compatible with near-normal life expectancy; **BRESHECK** carries high infant/childhood morbidity and mortality from brain/kidney anomalies, infections, and marrow involvement (PMID: 34655156). No formal survival statistics.
- **Morbidity/disability:** Dominated by **progressive visual impairment/blindness**, chronic skin disease, recurrent infections, and, in severe cases, intellectual disability and organ dysfunction; rare disabling contractures.
- **Complications:** Corneal scarring/blindness, secondary infections, growth failure; possible malignancy (single Hodgkin lymphoma case, PMID: 28654459).
- **Recovery potential:** No cure; features largely irreversible, though skin and corneal erosions can partially improve with therapy.
- **Prognostic factors: Residual MBTPS2 activity / genotype severity** is the principal determinant (PMID: 19361614); BRESHECK features predict poor outcome. No validated prognostic biomarkers.

12. Treatment

No curative/disease-modifying therapy; **symptomatic, multidisciplinary** (dermatology, ophthalmology, genetics ±). Suggested NCIT terms in parentheses.

Modality	Intervention	Evidence
Skin care	Emollients, urea keratolytics (NCIT: Emollient)	PMID: 38089015
Systemic retinoid	**Acitretin ~1 mg/kg** (NCIT:C29496) — partial cutaneous/corneal benefit; no effect on alopecia/photophobia	PMID: 16268889; PMID: 19689518
Ocular surface	Lubrication, prophylactic antibiotics, punctal occlusion, tarsorrhaphy	PMID: 32482964
Ocular surgery	**Amniotic membrane transplantation** (+ acitretin)	PMID: 21670910
Orthopedic	Soft-tissue release, Achilles lengthening for contractures	PMID: 41458897
Supportive	Infection management, low-vision rehab, growth/nutrition, genetic counseling	Multiple

Advanced/experimental therapies. No gene, cell, RNA, or targeted therapies are approved or in trials; no NCT-registered IFAP-specific interventional trials identified. Pharmacogenomics not applicable. Genotype (residual activity) may guide severity expectation/counseling, but no genotype-directed drug exists. Retinoid toxicity (mucocutaneous, hepatic, lipid, skeletal) and teratogenicity require monitoring.

13. Prevention

- **Primary prevention:** Not possible (monogenic germline). **Genetic counseling** and reproductive options (carrier testing, prenatal diagnosis, PGT-M) for at-risk families are the mainstay.
- **Secondary prevention:** Early ophthalmologic surveillance and **ocular-surface protection in infancy** to slow corneal vascularization and preserve vision; early skin care.
- **Tertiary prevention:** Infection prophylaxis/prompt treatment, vision rehabilitation, nutritional/growth support, management of BRESHECK complications.
- **Screening:** Cascade genetic testing of relatives; no population/newborn screening. Routine vaccination advisable given infection risk. Behavioral/public-health/environmental interventions are not applicable to causation.

14. Other Species / Natural Disease

- **Taxonomy / orthologs:** MBTPS2 is deeply conserved. Human *MBTPS2* (Taxon 9606); mouse *Mbtps2* (Taxon 10090; NCBI Gene 270669); *Drosophila S2P* (Taxon 7227); hamster ortholog underlies the classic M19 mutant cell line (Taxon 10029).
- **Natural disease in other species:** No naturally occurring IFAP-equivalent disease is catalogued in OMIA for companion animals or livestock; veterinary relevance is minimal.
- **Comparative biology / conservation:** The S2P–SREBP lipid-regulatory axis is conserved from insects to mammals; *Drosophila ds2p* nulls show lipid-auxotrophy phenotypes (PMID: 20935466), underscoring conserved essentiality.
- **Transmission:** Not applicable (non-infectious, non-zoonotic).

15. Model Organisms

Model	Type	Utility	Limitation
CHO-M19 cells	In vitro (mammalian)	**Principal functional assay** — complementation classifies variant pathogenicity/severity (PMID: 19361614; PMID: 34655156)	Does not reproduce tissue-level phenotype
Patient fibroblasts	In vitro (human)	Omics reveal fatty-acid/collagen signature; splicing/expression studies (PMID: 34093655; PMID: 37305034)	Not a whole-organism model
***Drosophila* dS2P / dSREBP nulls**	Invertebrate genetic	Conserved lipid-auxotrophy; dietary-lipid rescue (PMID: 20935466)	Does not model skin/eye phenotype

Gap: No dedicated *Mbtps2* mouse or zebrafish **IFAP disease model** was identified; whole-animal null models are expected to be lethal. Mechanistic inference relies on cellular complementation and orthologous invertebrate genetics. **Resources:** MGI (Mbtps2), FlyBase (S2P), Cellosaurus (M19/CHO), plus patient-derived cells.

Evidence Base

PMID	Contribution	Role
19361614	Gene identification; CHO-M19 complementation; activity–severity correlation	**Foundational** (F001, F002, F008)
34655156	BRESHECK variant impairs SREBP + abolishes UPR	Dual mechanism (F002, F003)
33743732	*MBTPS2* allelic disorder spectrum; RIP function	Supports (F002, F003)
38089015	Defines triad & inheritance; skin care	Supports (F003, F005)
16720460	X-inactivation → carrier mosaicism	Supports (F003)
32482964	Limbal stem-cell dysfunction (AS-OCT)	**Key ocular** (F004)
15370546	Progressive corneal vascularization; carrier sign	Supports (F004)
16268889	Acitretin partial response	**Key treatment** (F005)
21670910	Acitretin + amniotic membrane benefit	Supports (F005)
24313295	Variable expressivity; BRESHECK acronym	Supports (F006)
28654459	~40 cases; Hodgkin lymphoma report	Epidemiology (F006)
36539961	Intronic splice variant → exon-7 skipping	Diagnostics (F006)
20935466	Two-protease SREBP cascade; *Drosophila* dS2P	Pathway/model (F007, F008)
37267109	S2P–NF-κB immune link	**Mechanistic** (F007)
30431684	*GJB2* ichthyosis follicularis (DDx)	Differential (F009)
34093655; 37305034	S2P-mutant fibroblast omics (lipid/collagen)	Molecular signature (F009)
33742461; 41492963; 39912473	*SREBF1*-IFAP / HMD overlap	Differential/ heterogeneity
24452206	*TRPV3* vs *MBTPS2* Olmsted	Differential
19689518	Large Australian kindred; X-linked; acitretin	Inheritance/treatment
41458897	Atypical female; contractures; orthopedic surgery	Phenotype expansion

PMID	Contribution	Role
35396755	*GJB2* ichthyosis follicularis syndromes	Differential

Supported and Refuted Hypotheses

Supported: 1. IFAP1 is caused by partial LOF of *MBTPS2*, with residual activity inversely proportional to severity (PMID: 19361614; PMID: 34655156). 2. Photophobia results from a progressive keratopathy due to **limbal stem-cell dysfunction**, not a primary retinal defect (PMID: 15370546; PMID: 32482964). 3. Acitretin partially improves skin/corneal features but not alopecia/photophobia (PMID: 16268889; PMID: 21670910).

Refuted / not supported: - IFAP is **not** caused by environmental or infectious agents; no environmental or protective genetic modifiers are proven. - No animal model fully recapitulates the triad; claims of a definitive mouse/zebrafish IFAP model are **not supported** by retrieved literature.

Limitations and Knowledge Gaps

1. **Small evidence base.** With ~40 reported cases, all clinical claims derive from case reports/series; no controlled trials, no formal prevalence/incidence, and no validated QoL metrics exist.
2. **No animal disease model.** No *Mbtps2* mouse or zebrafish IFAP model was identified; mechanistic inference relies on CHO-M19 cells, patient fibroblasts, and *Drosophila* — none of which reproduce the skin/eye phenotype.
3. **Genotype–phenotype resolution is incomplete.** Although residual activity correlates with severity, identical variants can produce divergent phenotypes (PMID: 24313295), implying unidentified modifiers or stochastic X-inactivation effects.
4. **Treatment evidence is anecdotal.** Acitretin benefit rests on individual cases; optimal dosing, long-term outcomes, and ocular-therapy standardization are undefined.
5. **Uncertain associations.** The single Hodgkin-lymphoma report does not establish a malignancy risk; the S2P–NF-κB immune link is mechanistically plausible but not clinically proven in IFAP patients.

6. **Citation caveat.** One omics snippet (PMID: 34093655) was flagged as title-derived during validation; the omics conclusion should be treated as supported primarily by the paired PMID: 37305034.

Proposed Follow-up Experiments / Actions

1. **Generate a conditional *Mbtps2* hypomorphic mouse** (epidermis- and cornea-specific) to establish the first mammalian IFAP disease model and test whether residual-activity gradients recapitulate the human severity continuum.
2. **Single-cell / spatial transcriptomics of IFAP skin and limbus** to define cell-type-specific SREBP/ATF6 target-gene failure and confirm limbal stem-cell depletion at molecular resolution.
3. **Systematic variant-function mapping** in the CHO-M19 assay for all reported *MBTPS2* variants to build a quantitative activity-vs-severity calibration usable for prognostic counseling.
4. **Prospective natural-history registry** (multinational, given rarity) capturing standardized ophthalmic, dermatologic, and QoL endpoints.
5. **Pilot limbal stem-cell / amniotic-membrane protocols** with pre-specified visual-acuity endpoints to move ocular management beyond anecdote.
6. **Lipidomic/metabolomic profiling** of patient skin and serum to test whether topical lipid replacement (cholesterol/fatty-acid supplementation) can bypass the SREBP defect — a mechanistically rational, low-risk therapeutic hypothesis.
7. **Evaluate innate-immune function** (NF-κB responsiveness) in patient monocytes to determine whether recurrent infections warrant prophylactic strategies.

Report compiled from 9 confirmed findings and 28 reviewed publications. Evidence classes: human clinical (case reports/series), in vitro (CHO-M19 complementation, mini-gene/splicing assays, IHC), invertebrate model (Drosophila), and computational/omics. PMIDs cited inline.
