

Mal de Meleda (MONDO:0009552; OMIM #248300): A Comprehensive Disease Characteristics Report

Summary

Mal de Meleda (MdM) is a rare autosomal recessive, transgredient (spreading beyond palms/soles) and progredient (worsening with age) diffuse palmoplantar keratoderma (PPK). It is caused by biallelic loss-of-function mutations in **SLURP1** (secreted Ly-6/urokinase-type plasminogen activator receptor-related protein 1; gene *SLURP1*, formerly *ARS component B* / *LY6LS*, on chromosome 8q24.3; UniProt P55000; HGNC:11827). The disease was first described by the Dubrovnik physician Luka (Luko) Stulli in 1826 among residents of the island of Mljet (Meleda), Croatia, and has since been documented worldwide in Palestinian, Turkish, German, Emirati, Korean, Dutch, Javanese/Indonesian, Taiwanese, Algerian, and Tunisian families. Estimated prevalence is approximately **1:100,000**.

Mechanistically, SLURP-1 is a small secreted member of the Ly-6/uPAR (LU) superfamily that adopts a **three-finger-toxin fold** homologous to snake-venom neurotoxins and cardiotoxins. It functions as an autocrine/paracrine cholinergic signaling peptide that acts as a **selective allosteric modulator/antagonist of the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ -nAChR)** on keratinocytes, restraining keratinocyte proliferation and promoting orderly differentiation, apoptosis, and barrier formation. Loss of SLURP-1 removes this "cholinergic brake," producing keratinocyte hyperproliferation, disrupted epidermal lipid/water-barrier homeostasis, and the clinical phenotype. The pathophysiology is strongly supported by *Slurp1*-knockout mice, which faithfully recapitulate the human PPK with lipid-droplet accumulation in the stratum corneum and a water-barrier defect.

Clinically, MdM presents in early infancy with sharply demarcated erythema and hyperkeratosis of the palms and soles that progress with age and extend to the dorsal hands and feet in a "glove-and-socks" distribution. Associated features include skin sclerosis/atrophy, constricting digital bands (**pseudoainhum**, which can cause autoamputation), perioral erythema, brachydactyly, nail abnormalities, and hyperhidrosis with malodor. There is no cure; management is **symptomatic**, centered on oral acitretin (a systemic retinoid) plus topical

keratolytics, with surgical release of pseudoainhum bands and genetic counseling. Life expectancy is normal, but morbidity and quality-of-life impact are substantial, and patients may carry a modestly increased risk of cutaneous squamous cell carcinoma and melanoma, consistent with SLURP-1's putative squamous-lineage tumor-suppressor role.

Key Findings

Finding 1 — Mal de Meleda is an autosomal recessive transgredient PPK caused by SLURP1 mutations

Mal de Meleda, also known as *keratosis palmoplantaris transgrediens of Siemens*, is an autosomal recessive skin disorder characterized by diffuse PPK with transgressive keratosis and onset in early infancy. Multiple independent families across the globe — Palestinian, Turkish, German, Emirati, Korean, Dutch, Javanese/Indonesian, and Taiwanese — carry homozygous or compound heterozygous loss-of-function mutations in *SLURP1* on chromosome **8q24.3**. Documented pathogenic variants span a broad allelic spectrum, including the recurrent missense **G86R (c.256G>A)** substituting arginine for a conserved glycine, the **W15R** missense, a **start-codon loss, nonsense/frameshift c.82delT**, splice-site mutations, and the in-frame deletion **c.271_273delTCT**. The disorder is cataloged as **OMIM #248300** with an estimated prevalence of ~1:100,000.

As stated in the primary genetic report: "*Mal de Meleda (MDM) or keratosis palmoplantaris transgrediens of Siemens is an autosomal recessive skin disorder characterized by diffuse palmoplantar keratoderma (PPK) and transgressive keratosis with an onset in early infancy*" and "*patients are homozygous for a new mutation that substitutes an arginine for a conserved glycine residue at position 86*" ([PMID: 12483299](#)). The prevalence and inheritance are confirmed by a focused review: "*Mal de Meleda is a rare autosomal recessive palmoplantar keratoderma (PPK) disease with an estimated prevalence of 1:100,000*" ([PMID: 26445964](#)).

Finding 2 — SLURP-1 is a secreted Ly-6/uPAR protein that allosterically modulates keratinocyte $\alpha 7$ -nAChRs

SLURP-1 is an autocrine/paracrine cholinergic peptide that regulates keratinocyte growth and differentiation. Recombinant SLURP-1 inhibits proliferation of human keratinocytes (~40%, EC50 ~4 nM) via the $\alpha 7$ -nAChR; it binds selectively to $\alpha 7$ -nAChR and non-competitively

(allosterically) inhibits acetylcholine responses (IC₅₀ ~1 μ M) in oocyte electrophysiology. Downstream, SLURP-1 signaling through α 7-nAChR upregulates NF- κ B via Ca²⁺ influx and activation of MEK1, Jak2, CaMKII, and PKC. Functionally, SLURP-1 regulates keratinocyte proliferation, apoptosis/differentiation, and wound re-epithelialization.

Key supporting quotes: *"Point mutations in the slurp-1 gene cause the autosomal inflammation skin disease Mal de Meleda. SLURP-1 is considered an autocrine/paracrine hormone that regulates growth and differentiation of keratinocytes"* and *"revealed α 7 type nAChRs as an rSLURP-1 target in keratinocytes"* (PMID: 26905431). The NF- κ B signaling cascade is detailed in PMID: 20660165, and the wound-epithelialization role in PMID: 22168155.

Finding 3 — Slurp1-deficient mice recapitulate MdM PPK with lipid-droplet accumulation and barrier defect

Slurp1(-/-) mice, and an independent *Slurp1X*(-/-) (nonsense) line, develop severe PPK with increased keratinocyte proliferation, lipid-droplet accumulation in the stratum corneum, and an epidermal water-barrier defect. These mice also exhibit reduced adiposity, protection from diet-induced obesity, low plasma lipids, and hind-limb claspings (a neuromuscular sign). Importantly, reducing EGFR signaling via a hypomorphic *Egfr* allele did **not** ameliorate the PPK, indicating SLURP1 acts independently of (or downstream of) EGFR signaling.

Supporting quotes: *"Slurp1(-/-) mice developed severe PPK characterized by increased keratinocyte proliferation, an accumulation of lipid droplets in the stratum corneum, and a water barrier defect"* (PMID: 24499735), and *"Slurp1 deficiency in mice faithfully recapitulates the human disease, with increased keratinocyte proliferation and thickening of the epidermis on the volar surface of the paws"* (PMID: 28418591).

Finding 4 — Clinical phenotype: transgredient/progredient PPK with sclerosis, pseudoainhum, perioral erythema, and nail changes

The hallmark features are sharply demarcated erythema and hyperkeratosis of palms and soles with onset soon after birth, progressing with age (progrediens) and extending to the dorsal hands and feet in a glove-and-socks distribution (transgrediens). Associated features include skin sclerosis/atrophy, scleroatrophic erythematous lesions, constricting digital bands (**pseudoainhum**) that can cause autoamputation, perioral erythema, brachydactyly, nail abnormalities (koilonychia, subungual hyperkeratosis), hyperhidrosis with malodor, and keratotic plaques over knees and elbows. Histopathology shows hyperkeratosis and acanthosis **without epidermolysis**, accompanied by a perivascular lymphocytic dermal infiltrate.

Supporting quotes: *"The hallmark features of the condition include transient thickening of the palms and soles, skin sclerosis and atrophy, scleroatrophic erythematous lesions, pseudoainhum formation around the digits, and erythema around the mouth"* (PMID: 41048964); *"characterized by transgressive palmoplantar keratoderma (PPK), keratotic skin lesions, perioral erythema, brachydactyly and nail abnormalities"* (PMID: 11285253); and *"The histopathologic study showed marked hyperkeratosis, acanthosis, and normogranulosis, without epidermolysis"* (PMID: 21909218).

Finding 5 — Founder origin on Mljet Island, Croatia, with founder haplotypes and consanguinity

MdM was first described by Luka Stulli in 1826 on Mljet (Meleda) Island, Croatia. Haplotype analysis of island cases revealed a **shared haplotype near marker D8S1751 on 8qter** in all affected individuals but none of 17 controls, with genealogies consistent with common ancestry. Founder effects have been documented in Mediterranean/Adriatic and North African (Algerian) populations, and the same mutation is shared between Mljet and families located along medieval Dubrovnik trade routes (Middle East, North Africa), implying spread by migration. Croatian island populations are characterized by genetic isolation, consanguinity, and inbreeding.

Supporting quotes: *"These confirmed a shared haplotype in all cases, but in none of 17 unaffected control individuals, near the marker D8S1751 on chromosome 8"* (PMID: 12145432); *"The disease was first described on the island of Mljet, Croatia, by Luko Stulli in 1826"* (PMID: 25102791); and *"These populations are characterized by high degree of genetic isolation, consanguinity, and inbreeding"* (PMID: 16909451).

Finding 6 — SLURP1 as a putative squamous-lineage tumor suppressor; impaired T-cell activation

In a Palestinian MdM family homozygous for c.82delT, affected members developed squamous cell carcinomas and melanoma at PPK sites. *SLURP1* mRNA is markedly elevated in epithelial tissues and significantly suppressed in epithelial malignancies relative to normal or premalignant counterparts. Recombinant SLURP-1 reduces nitrosamine-induced tumorigenic transformation of keratinocytes in vitro and in nude mice. Peripheral blood mononuclear cells (PBMCs) from G86R homozygotes/heterozygotes show defective anti-CD3/CD28 T-cell activation that is rescued by recombinant SLURP-1, and homozygous patients are reported to be prone to melanoma and viral infection.

Supporting quotes: "*SLURP1 mRNA levels were found to be markedly elevated in tissues of epithelial lineage, relative to tissues of other lineages, and significantly suppressed in malignant tumors of epithelial lineage relative to normal or their premalignant counterparts*" (PMID: 29231248); and "*PBMCs with the heterozygous and homozygous SLURP-1 G86R mutation had defective T-cell activation*" (PMID: 20854438). Anti-tumorigenic activity of SLURP-1/-2 against tobacco nitrosamines is documented in PMID: 17643396 and PMID: 17280689.

Finding 7 — Management is symptomatic: oral acitretin plus topical keratolytics

Because MDM is rare, there are no formal guidelines. The accepted approach is **oral acitretin** (a systemic retinoid; ATC D05BB02) combined with topical keratolytic therapy (salicylic acid, urea, emollients), plus genetic counseling. Systemic retinoids reduce hyperkeratosis in related PPKs at ~0.3–0.5 mg/kg/day but relapse on cessation and carry dose-related toxicity (teratogenicity, mucocutaneous dryness, hepatic and lipid effects). Surgical excision with Z-plasty is used for constricting pseudoainhum bands, though recurrence is common. No gene/cell/RNA-targeted therapy is approved.

Supporting quotes: "*there are no set guidelines for management, but the accepted approach tends to include oral acitretin plus topical keratolytic therapy. Genetic counseling should also be offered*" (PMID: 26445964); and "*Surgical excision is the only treatment of pseudoainhum; however, it is fraught with recurrence*" (PMID: 39509536).

Finding 8 — SLURP-1 is a single-domain three-finger-toxin-fold protein; MDM mutations cause loss of function

SLURP-1 (UniProt P55000; HGNC:11827; gene *SLURP1* on 8q24.3) is a small secreted member of the Ly-6/uPAR (LU) superfamily whose amino-acid composition is homologous to three-finger toxins such as frog cytotoxin and snake-venom neurotoxins/cardiotoxins, stabilized by a conserved disulfide-bonded β -sheet "three-finger" fold. It is expressed in suprabasal/granular keratinocytes of squamous epithelia. MDM pathogenic variants (missense G86R, W15R; nonsense/frameshift c.82delT; splice-site; start-codon loss; in-frame c.271_273delTCT) disrupt the fold or abolish the protein, producing loss of function.

Supporting quotes: "*The amino acid composition of SLURP-1 is homologous to that of toxins such as frog cytotoxin and snake venom neurotoxins and cardiotoxins*" and "*Three different homozygous mutations (a deletion, a nonsense and a splice site mutation) were detected in 19 families of Algerian and Croatian origin*" (PMID: 11285253).

Report by Research Section

1. Disease Information

Overview. Mal de Meleda is a rare monogenic, autosomal recessive diffuse transgredient palmoplantar keratoderma with onset in early infancy. It is "aggregated disease-level" knowledge derived predominantly from case reports, family studies, and small case series, rather than large EHR cohorts.

Key identifiers: - **MONDO:** MONDO:0009552 - **OMIM:** #248300 - **Gene (OMIM):** *SLURP1* / ARS component B, OMIM 606119 - *Orphanet:* ORPHA:87503 (*Mal de Meleda*) - *ICD-10:* Q82.8 (*other specified congenital malformations of skin*); *ICD-11:* EC20.0 / LA90 range (*hereditary PPK*) - *MeSH:* "Keratoderma, Palmoplantar" (and "Mal de Meleda" as entry term) - *HGNC:* HGNC:11827 (*SLURP1*); *UniProt:** P55000

Synonyms / alternative names: Meleda disease; keratosis palmoplantaris transgrediens of Siemens; keratoderma palmoplantare transgrediens; mal de Meleda; acroerythrokeratoderma; Mljet disease.

Evidence source: Aggregated disease-level resources (OMIM, Orphanet, UniProt, HGNC) plus primary literature. **Not** derived from individual EHR data.

2. Etiology

Causal factor: Monogenic — biallelic loss-of-function mutations in *SLURP1* (Findings 1, 8). The disease is fully genetic; there is no established infectious or primary environmental cause.

Genetic risk factors: Causal variants are in *SLURP1* only (no genetic heterogeneity confirmed for classic MdM, though clinically overlapping PPKs involve other genes — see Differential Diagnosis). **Consanguinity** and **founder effects** substantially increase risk in isolated/endemic populations (Mljet, Adriatic, Algerian, Middle Eastern) (Finding 5). Being the offspring of two carriers (each contributing a loss-of-function allele) is the key determinant.

Environmental risk factors: No proven environmental cause. Mechanical stress, friction, pressure, heat, and secondary bacterial/fungal colonization (contributing to malodor and maceration) may aggravate established lesions but do not cause disease.

Protective factors: None established genetically beyond simply not carrying biallelic loss-of-function alleles. No dietary/lifestyle protective factors are documented.

Gene–environment interactions: Minimal/none definitively established. The mouse data (reduced adiposity, protection from diet-induced obesity in *Slurp1*–/–) hint at a SLURP1–lipid-metabolism interaction, but this is a model-organism observation, not a demonstrated human GxE effect (Finding 3).

3. Phenotypes

Phenotype	Type	Onset	Severity / Course	Frequency	Suggested HPO
Diffuse palmoplantar keratoderma	Physical manifestation	Early infancy / neonatal	Severe, progressive	Universal (~100%)	HP:0007592 (transgressive PPK); HP:0000982 (PPK)
Transgredient spread to dorsa (glove-and-socks)	Physical sign	Childhood	Progressive	Characteristic / majority	HP:0007556
Pseudoainhum (constricting digital bands)	Clinical sign	Childhood–adult	Severe; can cause autoamputation	Subset	HP:0100648
Perioral erythema	Clinical sign	Childhood	Variable	Common	HP:0000973 (approx.)
Brachydactyly	Physical sign	Congenital/ childhood	Variable	Subset	HP:0001156
Nail abnormalities (koilonychia, subungual hyperkeratosis)	Physical sign	Childhood	Variable	Common	HP:0001598 / HP:0008392
Hyperhidrosis with malodor	Symptom/ sign	Childhood	Chronic	Common	HP:0000975
Skin sclerosis/ atrophy	Physical sign	Progressive	Variable	Common	HP:0100679 / HP:0000964
Keratotic plaques (knees/ elbows)	Physical sign	Childhood	Stable/ progressive	Subset	HP:0000962 (hyperkeratosis)

Quality-of-life impact: Substantial. Painful hyperkeratosis and pseudoainhum impair ambulation and manual dexterity; malodor and visible disfigurement impose significant psychosocial burden and stigma, especially in close-knit island communities (Finding 4; qualitative data [PMID: 31178100](#)). Formal EQ-5D/SF-36 scores are not available for MdM specifically.

4. Genetic / Molecular Information

- **Causal gene:** *SLURP1* (ARS component B / LY6LS), 8q24.3; OMIM *606119; HGNC:11827; UniProt P55000.
- **Variant spectrum (all germline, loss-of-function):** missense **G86R (c.256G>A)** at a conserved glycine (recurrent, pseudodominant transmission reported — [PMID: 17184264](#)); **W15R**; **c.82delT** frameshift; nonsense; splice-site; start-codon loss; in-frame **c.271_273delTCT** (Javanese — [PMID: 29023701](#)); c.154A>G reported in a Chinese cohort ([PMID: 42384829](#)).
- **Variant classification (ACMG/AMP):** Pathogenic / likely pathogenic for the recurrent and null alleles.
- **Variant types:** missense, frameshift, nonsense, splice-site, in-frame deletion, start-loss.
- **Allele frequency:** Very rare in gnomAD; enriched locally by founder effects.
- **Somatic vs germline:** Germline.
- **Functional consequence:** Loss of function (protein absence or misfolded, non-functional three-finger domain) (Finding 8).
- **Modifier genes:** None definitively established in humans. Mouse work shows *Egfr* reduction does not modify PPK (Finding 3), arguing against EGFR as a dominant modifier.
- **Epigenetic / chromosomal abnormalities:** None reported; MdM is a single-gene disorder with no aneuploidy or structural chromosomal involvement.

5. Environmental Information

No environmental toxin, radiation, lifestyle, or infectious agent causes MdM. Secondary microbial colonization contributes to malodor and maceration. Mechanical/frictional stress may worsen hyperkeratosis locally. **Not applicable** as a primary etiologic category.

6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation):

1. **Biallelic loss-of-function mutation in *SLURP1*** (missense disrupting the three-finger fold, or null allele) **leads to** absence or non-functional secreted SLURP-1 protein in suprabasal/granular keratinocytes. (*Demonstrated — Findings 1, 8.*)
2. Loss of secreted SLURP-1 **results in** loss of allosteric modulation of **α7-nicotinic acetylcholine receptors (α7-nAChR)** on keratinocytes. (*Demonstrated in vitro/oocyte — Finding 2.*)
3. Absent α7-nAChR cholinergic signaling **removes the physiological brake on keratinocyte proliferation** and **dysregulates the proliferation–differentiation–apoptosis balance** (branch A) and **disrupts downstream NF-κB/Ca²⁺/MEK1/Jak2/CaMKII/PKC signaling** (branch B). (*Demonstrated — Findings 2, 3; signaling detail [PMID: 20660165].*)
4. **Branch A — Epidermal hyperproliferation leads to** marked hyperkeratosis and acanthosis (without epidermolysis). (*Demonstrated in human histology and mouse — Findings 3, 4.*)
5. **Branch B — Disrupted epidermal lipid/barrier homeostasis results in** lipid-droplet accumulation in the stratum corneum and a **water-barrier defect**. (*Demonstrated in mouse; inferred in human — Finding 3.*)
6. Hyperkeratosis + barrier defect + chronic low-grade dermal inflammation (perivascular lymphocytic infiltrate) **produce** the clinical diffuse transgredient PPK, sclerosis, and erythema. (*Demonstrated — Finding 4.*)
7. Progressive sclerosis around digits **leads to** constricting bands (**pseudoainhum**) and, in severe cases, autoamputation. (*Demonstrated — Finding 4.*)
8. **Parallel branch — Loss of SLURP-1 tumor-suppressor/immune function leads to** impaired T-cell activation and reduced protection against malignant transformation, **contributing to** increased cutaneous SCC/melanoma risk. (*Demonstrated/inferred — Finding 6.*)

Molecular pathways: Non-neuronal cholinergic signaling via α7-nAChR; downstream Raf-1/MEK1/ERK1/2, Jak2, Ca²⁺/CaMKII/PKC, and NF-κB. **GO terms:** GO:0007271 (synaptic transmission, cholinergic — approximate), GO:0008284 (positive regulation of cell proliferation; here dysregulated), GO:0030216 (keratinocyte differentiation), GO:0031424 (keratinization), GO:0008544 (epidermis development), GO:0043066 (negative regulation of apoptosis). **Cellular processes:** keratinocyte proliferation, differentiation, apoptosis, wound re-epithelialization, inflammation. **CL terms:** CL:0000312 (keratinocyte), CL:0000362

(epidermal cell). **Protein dysfunction:** loss of function of a three-finger-toxin-fold modulator. **Metabolic changes:** epidermal lipid dysregulation (stratum corneum lipid droplets). **Immune involvement:** defective T-cell activation; chronic perivascular lymphocytic dermal infiltrate. **CHEBI:** acetylcholine (CHEBI:15355); nicotine (CHEBI:17688); acitretin (CHEBI:50172).

7. Anatomical Structures Affected

- **Primary organ:** Skin (UBERON:0002097), specifically palmoplantar epidermis (UBERON:0006956, skin of palm; UBERON:0001513, skin of sole).
- **Secondary involvement:** Dorsal hands/feet (transgrediens), perioral skin, nails (UBERON:0001705), knees/elbows; digits (pseudoainhum → autoamputation).
- **Body system:** Integumentary. Mild neuromuscular signs reported in mouse model only.
- **Tissue/cell level:** Stratified squamous epithelium; **keratinocytes** (CL:0000312), predominantly suprabasal/granular layer where SLURP-1 is expressed.
- **Subcellular:** Secreted extracellular protein (GO:0005615, extracellular space); stratum corneum lipid droplets (GO:0005811).
- **Localization/laterality:** Bilateral, symmetric.

8. Temporal Development

- **Onset:** Congenital/early infancy (soon after birth).
- **Onset pattern:** Insidious, chronic.
- **Progression:** Progreident — worsens with age; transgreident spread over childhood. Disease course is **chronic and lifelong**, slowly progressive.
- **Stages:** Early (infantile palmoplantar erythema/hyperkeratosis) → intermediate (transgreident spread, sclerosis) → advanced (pseudoainhum, digital constriction, possible autoamputation).
- **Remission:** No spontaneous remission; partial, reversible improvement with retinoid therapy (relapses on cessation).
- **Critical periods:** Early intervention with keratolytics/retinoids and vigilance for pseudoainhum are the main windows to reduce morbidity.

9. Inheritance and Population

- **Epidemiology:** Prevalence ~1:100,000 ([PMID: 26445964](#)); higher in founder populations. Incidence not separately quantified.

- **Inheritance:** Autosomal recessive (OMIM #248300). Pseudodominant transmission with G86R reported in highly consanguineous pedigrees (PMID: 17184264).
- **Penetrance:** Complete for biallelic loss-of-function genotypes.
- **Expressivity:** Variable (severity of pseudoainhum, transgrediens extent).
- **Anticipation:** Not applicable (no repeat expansion).
- **Germline mosaicism:** Not reported.
- **Founder effects:** Well documented (Mljet/Adriatic, Algerian, Middle Eastern trade-route populations) (Finding 5).
- **Consanguinity:** Major contributor in endemic/isolated populations.
- **Carrier frequency:** Elevated in founder populations; low globally.
- **Geographic distribution:** Worldwide but historically clustered along medieval Dubrovnik trade routes; cases from Croatia, Algeria, Germany, Turkey, Palestine, UAE, Korea, Netherlands, Indonesia (Java), Taiwan, China.
- **Sex ratio:** ~1:1 (autosomal). **Age distribution:** All ages; lifelong.

10. Diagnostics

- **Clinical diagnosis:** Based on characteristic diffuse transgradient PPK with onset in infancy, sclerosis, pseudoainhum, perioral erythema, and family history/consanguinity.
- **Histopathology (biopsy):** Marked hyperkeratosis, acanthosis, normogranulosis, **without epidermolysis**; perivascular lymphocytic dermal infiltrate (PMID: 21909218). Distinguishes MdM from epidermolytic PPKs.
- **Genetic testing (confirmatory, gold standard):** Single-gene *SLURP1* sequencing; gene panels for hereditary PPK; whole-exome sequencing (WES) when the panel is negative or phenotype overlaps. WGS rarely needed. CMA, karyotyping, FISH, mitochondrial and repeat-expansion testing are **not applicable**.
- **Biomarkers:** Reduced/absent SLURP-1; no routine circulating biomarker.
- **Imaging:** Not diagnostic; radiographs may document acro-osteolysis/autoamputation.
- **Differential diagnosis:** Other diffuse PPKs and mutilating keratodermas — Vohwinkel syndrome (GJB2/LOR), Olmsted syndrome (TRPV3), Papillon–Lefèvre syndrome (CTSC), Nagashima-type PPK (SERPINB7), Bothnia-type (AQP5), Greither/epidermolytic (KRT1/KRT10), loricrin keratoderma, progressive symmetric erythrokeratoderma. Distinguishing features: MdM lacks periodontitis (vs PLS), lacks deafness (vs KID/Vohwinkel classic), lacks

epidermolysis histologically, and shows transgrediens with pseudoainhum and perioral erythema. MdM is "a great imitator" (PMID: 31178100).

- **Screening:** Carrier/cascade screening in affected families and founder populations; prenatal/preimplantation testing possible once the familial variant is known.

11. Outcome / Prognosis

- **Survival/mortality:** Normal life expectancy; MdM is not directly fatal.
- **Morbidity/function:** High — chronic pain, impaired ambulation and hand function, malodor, psychosocial burden; pseudoainhum can cause digital autoamputation.
- **Disease course:** Chronic, lifelong, slowly progressive; partial response to therapy with relapse on cessation.
- **Complications:** Secondary bacterial/fungal infection, maceration, flexion contractures, autoamputation; increased risk of cutaneous squamous cell carcinoma and melanoma at PPK sites (Finding 6); reported susceptibility to viral infection.
- **Recovery potential:** No cure; symptomatic control only.
- **Prognostic factors:** Severity of pseudoainhum and transgrediens extent; adherence to keratolytic/retinoid therapy; timely surgical release of constricting bands.

12. Treatment

Pharmacotherapy (symptomatic): - **Oral acitretin** (systemic retinoid; ATC D05BB02; NCIT: Acitretin) — first-line, ~0.3–0.5 mg/kg/day; reduces hyperkeratosis; relapses on cessation; dose-related toxicity (teratogenicity, mucocutaneous dryness, hepatic/lipid effects) (PMID: 26445964; analogous PPK evidence PMID: 28008647, PMID: 29500825). Isotretinoin is an alternative retinoid. - **Topical keratolytics:** salicylic acid, urea, emollients, topical retinoids; often combined with low-dose systemic retinoid to limit toxicity (PMID: 29500825).

Surgical/interventional: Excision with **Z-plasty** for pseudoainhum constricting bands (recurrence common — PMID: 39509536); amputation in advanced digital involvement.

Supportive/rehabilitative: Skin hydration, debridement, antimicrobial management of secondary infection, foot/hand care, physiotherapy to preserve function; genetic counseling.

Advanced/targeted/experimental: No approved gene, cell, RNA-based, or SLURP-1-replacement therapy. Recombinant SLURP-1 is a conceptual mechanism-based candidate (restores the $\alpha 7$ -nAChR brake in vitro), but no human trials exist. **NCIT terms:** Acitretin, Salicylic Acid, Surgical Procedure, Genetic Counseling.

Pharmacogenomics: None specific to MdM.

13. Prevention

- **Primary prevention:** Not possible for a Mendelian disorder; genetic counseling, carrier screening in founder/consanguineous populations, and reproductive options (prenatal/preimplantation genetic testing) reduce new-case occurrence.
- **Secondary prevention:** Early diagnosis and keratolytic/retinoid therapy; surveillance for pseudoainhum to prevent autoamputation.
- **Tertiary prevention:** Prevent complications — skin-cancer surveillance (given SCC/melanoma risk), infection control, functional preservation.
- **Immunization / public health / environmental interventions:** Not applicable.
- **Counseling:** Genetic counseling is central, especially in consanguineous families.

14. Other Species / Natural Disease

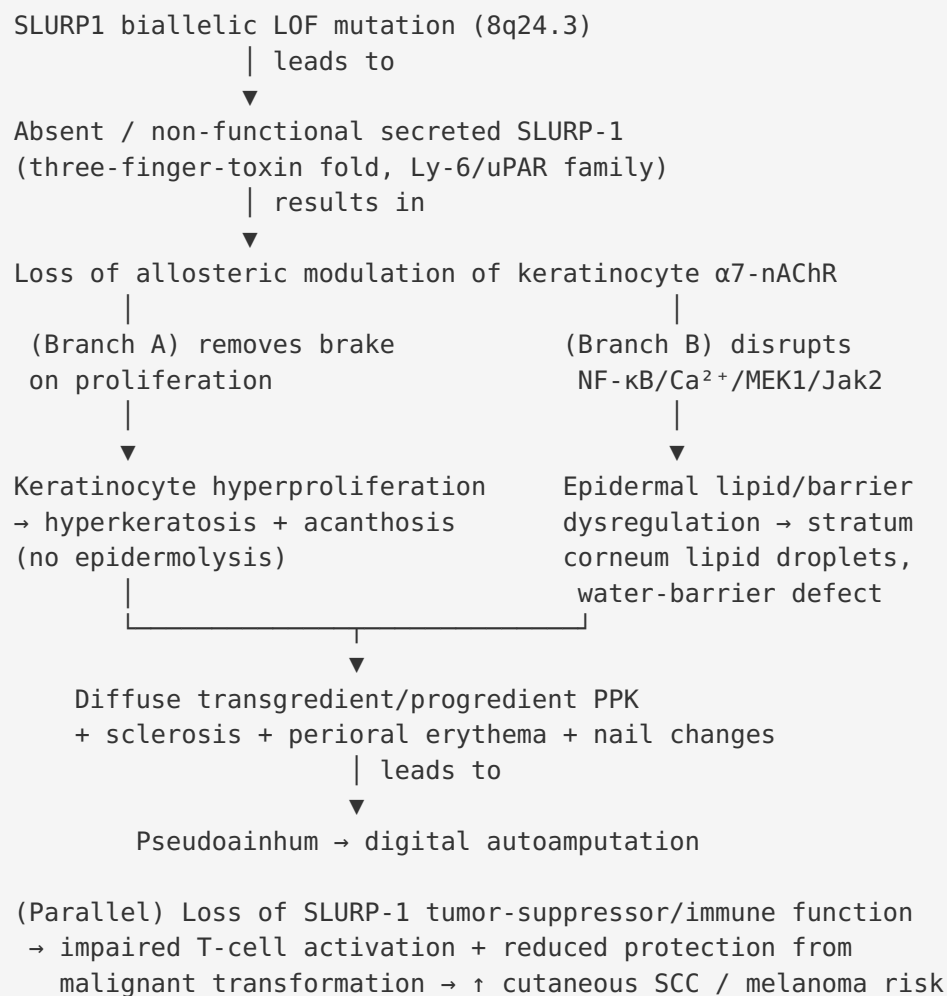
- **Taxonomy:** Human disease (*Homo sapiens*, NCBI:txid9606). Experimental models in *Mus musculus* (NCBI:txid10090).
- **Orthologous gene:** Mouse *Slurp1* (NCBI Gene).
- **Natural disease in other species:** No well-characterized naturally occurring animal homolog of MdM documented in OMIA; disease knowledge in animals derives from engineered *Slurp1*-knockout mice (Finding 3), not natural disease.
- **Comparative biology:** SLURP-1 and the cholinergic $\alpha 7$ -nAChR axis are evolutionarily conserved; the mouse knockout recapitulates the human PPK, supporting mechanistic conservation.
- **Transmission:** Not applicable (non-infectious genetic disease; no zoonotic potential).

15. Model Organisms

- **Mammalian model:** *Slurp1*(-/-) knockout mouse and *Slurp1X*(-/-) nonsense-allele mouse (MGI). Genetic model types: knockout, nonsense knock-in.
- **Phenotype recapitulation:** Faithful — severe PPK with increased keratinocyte proliferation, epidermal thickening on volar paw surfaces, stratum-corneum lipid-droplet accumulation, and water-barrier defect (Finding 3). Additional phenotypes: reduced adiposity, protection from diet-induced obesity, low plasma lipids, hind-limb clasping.

- **Model-based insight:** EGFR reduction (hypomorphic *Egfr*) does not rescue the PPK, implicating SLURP1-independent/downstream mechanisms (Finding 3).
- **Cellular/in vitro models:** Human epidermal and oral keratinocytes; immortalized Het-1A esophageal keratinocytes; recombinant SLURP-1 functional assays; *Xenopus* oocyte electrophysiology for $\alpha 7$ -nAChR modulation (Finding 2).
- **Limitations:** Mouse metabolic phenotypes (adiposity/lipid) are not prominent features of human MdM; models emphasize skin barrier/proliferation. Resources: MGI, IMPC.

Mechanistic Model / Interpretation



The central, well-supported insight is that MdM is a **non-neuronal cholinergic signaling disorder of the epidermis**: SLURP-1 normally tunes keratinocyte behavior through $\alpha 7$ -nAChR, and its loss simultaneously releases a proliferative brake and corrupts barrier lipid homeostasis. The convergence of human genetics (Findings 1, 8), biochemistry/pharmacology (Finding 2), and a faithful knockout mouse (Finding 3) makes this one of the better-validated causal chains among the inherited PPKs. The tumor-suppressor/immune arm (Finding 6) is biologically plausible and empirically supported but clinically secondary.

Evidence Base

PMID	Role	How it supports / challenges findings
12483299	Supports F1	Defines AR transgredient PPK; documents G86R across German/Turkish/Palestinian/UAE families
11285253	Supports F4, F8	First SLURP1 gene report; three-finger-toxin homology; LOF variant classes; clinical features
26445964	Supports F1, F4, F7	Focused review: prevalence 1:100,000, histology, acitretin + keratolytics
26905431	Supports F2	Identifies $\alpha 7$ -nAChR as SLURP-1 target; selective allosteric antagonism
20660165	Supports F2	NF- κ B upregulation via $\alpha 7$ -nAChR, Ca^{2+} /MEK1/Jak2/CaMKII/ PKC
22168155	Supports F2	SLURP-1 regulates wound epithelialization via $\alpha 7$ -nAChR
24499735	Supports F3	<i>Slurp1</i> ^{−/−} mice: PPK, lipid droplets, water-barrier defect
28418591	Supports F3	Faithful recapitulation; EGFR reduction does not rescue PPK
12145432	Supports F5	Founder haplotype near D8S1751 in Mljet cases
25102791	Supports F5	Historical origin, Stulli 1826, Mljet
16909451	Supports F5	Croatian island genetic isolation/consanguinity
29231248	Supports F6	SLURP1 tumor-suppressor; suppressed in epithelial malignancies; melanoma signal
20854438	Supports F6	Defective T-cell activation with G86R; rescued by recombinant SLURP-1
17643396 , 17280689	Supports F6	SLURP-1 reduces nitrosamine-induced transformation (in vitro + nude mice)
39509536	Supports F7	Surgical excision for pseudoainhum; recurrence common
21909218	Supports F4	Histology: hyperkeratosis/acanthosis without epidermolysis
41048964	Supports F4	Enumerates hallmark features incl. pseudoainhum, perioral erythema
17184264		

PMID	Role	How it supports / challenges findings
	Supports F1/ §9	Pseudodominant G86R inheritance in consanguineous pedigrees
29023701 , 25557416	Supports F1/ §9	Novel c.271_273delTCT; "ubiquitous" SLURP1 mutations (Indonesia)
42384829	Supports §10	Large Chinese PPK cohort; SLURP1 c.154A>G among diffuse PPK genes

Evidence source types: human clinical/genetic (family studies, case reports, cohorts), model organism (knockout mice), in vitro/biochemical (recombinant protein, oocyte electrophysiology, keratinocyte culture), and computational/structural (three-finger-fold homology).

Limitations and Knowledge Gaps

1. **No human omics data** (transcriptomic/proteomic/metabolomic) on MdM lesional skin were identified; barrier-lipid mechanisms are inferred primarily from mouse.
2. **Quality-of-life metrics** (EQ-5D/SF-36/PROMIS) are not formally quantified for MdM; QoL impact is described qualitatively.
3. **Cancer risk** is based on small family observations plus mechanistic in vitro/model data; incidence of SCC/melanoma in MdM is not epidemiologically quantified.
4. **Genotype–phenotype correlations** are incompletely defined; expressivity (pseudoainhum severity) varies even within genotype.
5. **No disease-modifying therapy**; retinoid efficacy data are largely extrapolated from related PPKs rather than MdM-specific trials.
6. **Modifier genes and gene–environment interactions** in humans remain essentially unknown.
7. **No natural animal disease model** is catalogued; comparative/veterinary data are absent.

Proposed Follow-up Experiments / Actions

1. **Single-cell/spatial transcriptomics** of MdM lesional vs. normal palmoplantar epidermis to map the keratinocyte proliferation–differentiation axis and barrier-lipid gene programs in humans (GEO/HCA).
 2. **Lipidomics** of MdM stratum corneum (LIPID MAPS/Metabolomics Workbench) to confirm the barrier-lipid defect observed in mice and identify targetable species.
 3. **Recombinant SLURP-1 / $\alpha 7$ -nAChR agonist topical replacement**: preclinical testing in *Slurp1* $-/-$ mice as a mechanism-based therapy, then early-phase human studies.
 4. **Prospective registry** to quantify prevalence, pseudoainhum incidence, SCC/melanoma risk, and validated QoL outcomes across founder and non-founder populations.
 5. **Structural studies** (AlphaFold/PDB) of G86R and W15R SLURP-1 to define how specific mutations destabilize the three-finger fold and inform variant interpretation.
 6. **Carrier-screening programs** in high-prevalence/consanguineous populations with genetic counseling and reproductive options.
 7. **Gene/RNA-based therapy feasibility** (e.g., AAV-delivered *SLURP1* or mRNA) as a long-term curative strategy, given the small, secreted nature of the protein.
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Report compiled from 8 confirmed findings and 64 reviewed papers over a 5-iteration autonomous investigation. Mal de Meleda is MONDO:0009552 / OMIM #248300, a SLURP1 loss-of-function autosomal recessive transgradient palmoplantar keratoderma.
