Olmsted Syndrome 2 (OLMS2, MONDO:0030961): A Comprehensive Disease Characterization

Causal gene: PERP (p53 apoptosis effector related to PMP-22; HGNC:17637; NCBI Gene 64065; UniProt Q96FX8; chromosome 6q23.3; reference transcript NM_022121.5; gene OMIM *609301)

Summary

Olmsted Syndrome 2 (OLMS2; MONDO:0030961) is an ultra-rare Mendelian keratinizing genodermatosis caused by germline mutations in *PERP*, a structural tetraspan membrane glycoprotein of the PMP22/EMP/MP20/claudin family that is an essential component of epidermal desmosomes. It is molecularly and mechanistically distinct from the more common, classically described Olmsted syndrome caused by gain-of-function mutations in *TRPV3* (OMIM #614594) and from X-linked *MBTPS2*-related Olmsted syndrome. The name "Olmsted syndrome 2" is a serial designation that does not itself name the gene; the defining feature of this entity is that its cause is *PERP*, a desmosomal adhesion protein, not an ion channel or a membrane-bound protease.

The disease has a striking dual-inheritance architecture that maps cleanly onto the position and nature of the *PERP* mutation. **Heterozygous C-terminal truncating variants (nonsense/frameshift) cause autosomal dominant disease** — severe, mutilating, transgredient palmoplantar keratoderma (PPK) combined with periorificial keratotic plaques — through a dominant-negative mechanism in which an unstable mutant protein is poorly incorporated into desmosomes, destabilizing them. In contrast, **biallelic (recessive) N-terminal truncations or missense variants cause milder disease** — generalized erythrokeratoderma/ichthyosis with PPK — through loss of PERP expression/function. The core lesion in both is structural: immature desmosomes lacking the normal electron-dense midline and impaired keratinocyte intercellular adhesion under mechanical stress.

Downstream of this adhesion failure, the epidermis becomes hyperproliferative with altered differentiation, and lesional skin shows increased EGFR and mTOR/RPS6 signaling. This downstream convergence provides the rationale for the emerging targeted therapies — the EGFR inhibitor **erlotinib** and the mTOR inhibitor **sirolimus** — alongside traditional retinoids, keratolytics, emollients, surgical release of constricting pseudoainhum bands, and pain/pruritus management. The condition is congenital or early-childhood in onset, chronic, progressive, and highly disabling but non-lethal in humans; it is diagnosed clinically and confirmed by exome/panel sequencing, with characteristic electron-microscopic desmosomal immaturity on skin biopsy. *Perp*-null mouse models recapitulate epithelial blistering and hyperproliferation, and additionally reveal a tumor-suppressor role in UV-induced skin squamous cell carcinoma.

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1. Disease Information

Overview. Olmsted syndrome (OS) is a rare genodermatosis classically defined by the combination of **bilateral mutilating transgredient palmoplantar keratoderma (PPK)** and **periorificial keratotic plaques**, with considerable clinical heterogeneity. *PERP*-related disease (OLMS2) is the specific molecular subtype caused by *PERP* mutations, first delineated by Duchatelet et al. in 2019 (PMID: 30321533).

> "Olmsted syndrome (OS) is a rare genodermatosis classically characterized by the combination of bilateral mutilating transgredient palmoplantar keratoderma (PPK) and periorificial keratotic plaques, but which shows considerable clinical heterogeneity." — PMID: 25886873

Key identifiers.

Resource	Identifier
Mondo	MONDO:0030961 (Olmsted syndrome 2 / OLMS2)
Causal gene	*PERP* — HGNC:17637; NCBI Gene 64065; UniProt Q96FX8; gene OMIM *609301
Orphanet	ORPHA:659 (Olmsted syndrome, umbrella)
Related (distinct)	TRPV3-Olmsted syndrome OMIM #614594; MBTPS2-related X-linked Olmsted syndrome
ICD-10	Q82.8 (other specified congenital malformations of skin) — mapped at the OS level
MeSH	No OLMS2-specific descriptor; indexed under keratoderma, palmoplantar

Synonyms / alternative names. OLMS2; PERP-related Olmsted syndrome; autosomal dominant PERP-related keratoderma.

Information source. The knowledge base entry is derived from **aggregated, disease-level resources** (OMIM, Orphanet, Mondo) and primary literature (case series and functional studies), not individual EHR patient records. Given the ultra-rarity of the disease, the evidence is drawn from a small number of kindreds and functional/model-organism studies.

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2. Etiology

Disease causal factors. OLMS2 is a **monogenic (Mendelian) genetic disorder** caused by germline mutations in *PERP*. There is no environmental, infectious, or acquired cause of the core disease. *PERP* encodes a desmosomal component, and its disruption is both necessary and sufficient to produce the keratoderma phenotype.

> "...mutations in PERP, encoding a crucial component of desmosomes, cause both dominant and recessive human keratoderma" — PMID: 30321533

Genetic risk factors. The causal variants are the *PERP* truncating/missense mutations themselves (detailed in Section 4). There are no known common susceptibility loci — the disease is fully penetrant Mendelian, not multifactorial.

Environmental risk factors. None established as causal. Mechanical stress is relevant as a *modifier/trigger of manifestation* at the cellular level (impaired adhesion manifests "upon mechanical stress," PMID: 30321533), consistent with the acral (palmoplantar) distribution of the most severe lesions, which are the body sites under greatest frictional load. In recessive biallelic cases, cutaneous fungal infection has been reported to coincide with psoriasiform plaque flares (PMID: 34863005), suggesting infection may act as a secondary trigger/aggravator rather than a cause.

Protective factors. No genetic or environmental protective factors have been identified. This is expected for a rare Mendelian disorder with high penetrance.

Gene–environment interactions. Not formally studied. The acral/periorificial and friction-prone distribution of lesions is consistent with mechanical load interacting with the underlying adhesion defect, but this is inferred, not demonstrated.

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3. Phenotypes

The core clinical phenotype of Olmsted syndrome, and specifically PERP-related disease, comprises:

Phenotype	Type	Suggested HPO	Onset	Severity	Frequency
Bilateral mutilating transgredient palmoplantar keratoderma	Physical manifestation / clinical sign	HP:0000982 (Palmoplantar keratoderma)	Birth / early childhood	Severe	Defining (near-100%)
Periorificial keratotic plaques	Clinical sign	HP:0011220 (periorificial hyperkeratosis type)	Early childhood	Severe	Defining
Pseudoainhum (constricting fibrous bands, autoamputation risk)	Physical manifestation	HP (constriction of digit)	Childhood, progressive	Severe	Frequent in severe OS
Hair abnormalities (alopecia/sparse hair)	Clinical sign	HP:0001596 (Alopecia)	Variable	Variable	Frequent
Nail abnormalities	Clinical sign	HP:0001597 (Abnormality of the nail)	Variable	Variable	Frequent
Oral leukokeratosis	Clinical sign	HP:0011817 (oral leukoplakia type)	Variable	Mild–moderate	Frequent
Corneal defects	Clinical sign	HP:0000481 (Abnormality of the cornea)	Variable	Variable	Frequent
Recurrent infections	Clinical sign	HP:0002719 (Recurrent infections)	Variable	Variable	Frequent
Pain	Symptom	HP:0012531 (Pain)	Early	Variable, can be severe	Variable
Pruritus (itching)	Symptom	HP:0000989 (Pruritus)	Early	Variable, can be severe	Variable
				Milder	

Phenotype	Type	Suggested HPO	Onset	Severity	Frequency
Generalized erythrokeratoderma (recessive form)	Physical manifestation	HP:0001055 (Erythrokeratoderma)	Birth/ infancy		Recessive cases

> "Suggestive features: PPK with pseudoainhum and periorificial keratotic plaques. Frequently associated features include hair and nail abnormalities, leukokeratosis, corneal default and recurrent infections. Pain and itching are variable but can be severe." — PMID: 25886873

Genotype–phenotype gradient of severity. Dominant C-terminal truncations produce the most severe, mutilating periorificial + palmoplantar keratoderma (OLMS2 proper); homozygous N-terminal truncation produces widespread erythrokeratoderma; biallelic missense variants produce the mildest ichthyosis/erythrokeratoderma with psoriasiform plaques (PMID: 30321533; PMID: 34863005).

Quality of life impact. The mutilating PPK with pseudoainhum, severe pain, and pruritus produces profound functional disability affecting ambulation, manual dexterity, and daily living; QoL in treatment studies has been assessed with pain/pruritus visual analog scales (VAS) and the Children's Dermatology Life Quality Index (CDLQI) (PMID: 31895414). No disease-specific EQ-5D/SF-36 data exist given rarity.

4. Genetic / Molecular Information

Causal gene. *PERP* (HGNC:17637; NCBI Gene 64065; UniProt Q96FX8; chromosome 6q23.3; transcript NM_022121.5; OMIM *609301). PERP is a tetraspan membrane glycoprotein of the PMP22/EMP/MP20/claudin family localized to epidermal desmosomes and is a direct transcriptional target of p63.

Pathogenic variants and genotype–phenotype correlation.

Zygosity / variant class	Example variants	Mechanism	Phenotype
Heterozygous C-terminal truncating (nonsense/ frameshift)	C-terminal truncations	Dominant-negative: unstable protein poorly incorporated into desmosomes	**Dominant Olmsted syndrome (OLMS2)** — severe periorificial + palmoplantar keratoderma
Homozygous N-terminal truncation	N-terminal truncation	Loss of expression	Widespread erythrokeratoderma with expansion of epidermal differentiation markers
Biallelic recessive missense	c.89T>C p.Leu30Pro; c.466G>C p.Gly156Arg	Loss/partial loss of function	Milder ichthyosis/ erythrokeratoderma, PPK, psoriasiform plaques (± fungal infection)

> "Monoallelic nonsense mutations cause Olmsted syndrome with severe periorificial keratoderma and palmoplantar keratoderma (PPK). Biallelic recessive frameshift and missense mutations are associated with milder forms of the disease, including generalised erythrokeratoderma and PPK." — PMID: 34863005
>
> "Homozygosity for an N-terminal truncation ablates expression and causes widespread erythrokeratoderma, with expansion of epidermal differentiation markers." — PMID: 30321533

Exact variant nomenclature (recessive, milder cases).

> "two novel biallelic PERP variants, NM_022121.5, c.89T > C, p.Leu30Pro and c.466G > C, p.Gly156Arg" — PMID: 34863005

Variant classification (ACMG/AMP). Truncating variants in a gene with an established loss-of-function/dominant-negative mechanism are classified **pathogenic/likely pathogenic**; the recessive missense variants were reported as novel disease-associated (likely pathogenic in the context of biallelic inheritance and phenotype segregation).

Allele frequency. Pathogenic *PERP* variants are private/rare and largely **absent from gnomAD** at appreciable frequency. No founder allele or recurrent hotspot has been established.

Somatic vs germline. All disease-causing *PERP* variants are **germline**. No somatic *PERP* disease association exists for OLMS2. (Of note, *PERP* loss is relevant to somatic skin carcinogenesis in model systems — see Sections 6 and 15 — but that is a tumor-suppressor context, not OLMS2 itself.)

Functional consequences. Dominant C-terminal truncation = **dominant-negative** (unstable protein incorporated into desmosomes, destabilizing them); N-terminal truncation = **loss of function** (no expression); recessive missense = partial/complete loss of function.

Modifier genes. None established.

Epigenetic information. *PERP* is transcriptionally controlled by the master epithelial regulator **p63** (and p53); SATB2 can attenuate p63-driven *perp* expression (PMID: 21965674). No disease-specific DNA-methylation or histone-modification data for OLMS2 exist.

Chromosomal abnormalities. None — OLMS2 is a single-gene point-mutation disorder, not a copy-number/structural disorder.

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5. Environmental Information

- **Environmental factors:** None causal. Mechanical friction plausibly aggravates acral lesions given the adhesion defect (inferred).
- **Lifestyle factors:** None established.
- **Infectious agents:** Not causal. Cutaneous **fungal infection** was reported to coincide with psoriasiform plaque flares in biallelic *PERP* disease (PMID: 34863005) — a secondary trigger/aggravator — and recurrent infections are a frequently associated feature of OS generally (PMID: 25886873), likely secondary to barrier compromise.

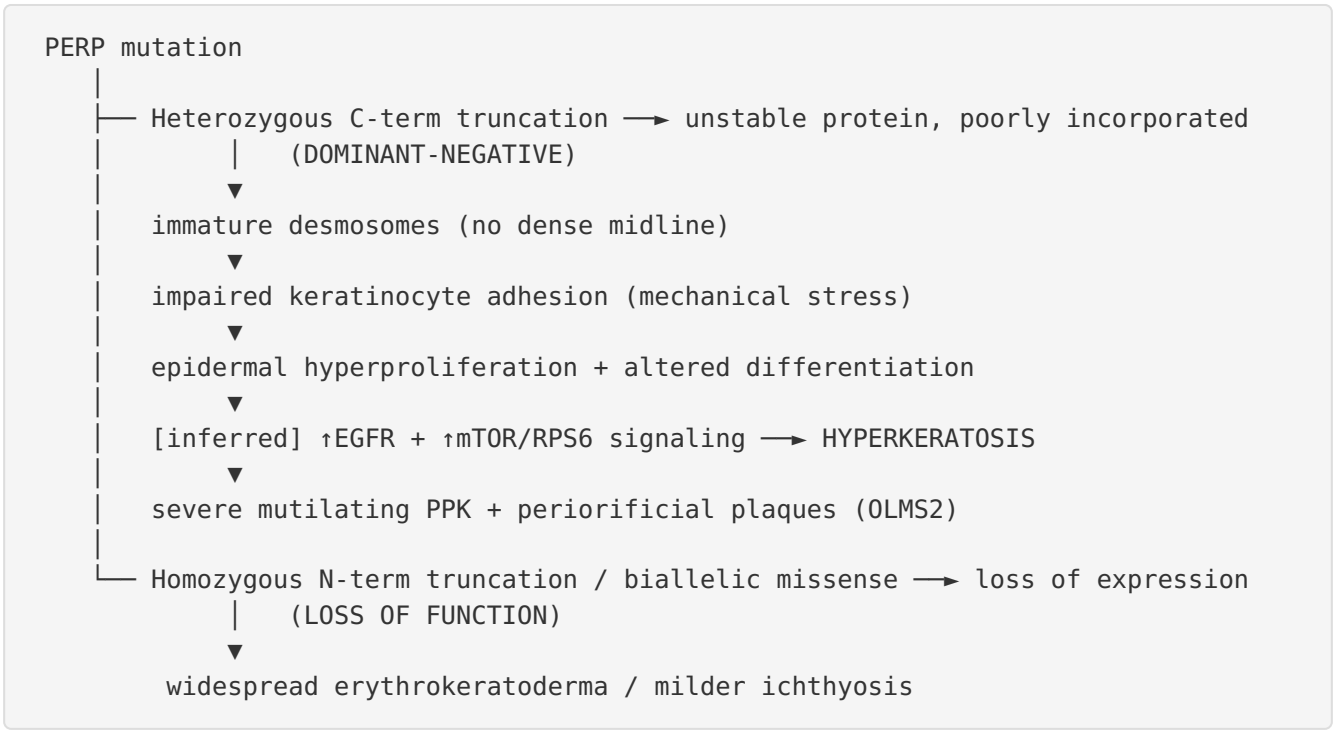
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6. Mechanism / Pathophysiology

Ordered causal chain

1. A **heterozygous C-terminal truncating *PERP* mutation** produces an unstable PERP protein that is poorly incorporated into desmosomes (dominant-negative). *[Human; PMID: 30321533]*
2. This **leads to immature desmosomes lacking a dense midline** (electron microscopy), while other desmosomal components localize normally. *[Human; PMID: 30321533]*
3. This **results in impaired keratinocyte intercellular adhesion upon mechanical stress** *[Human/in vitro; PMID: 30321533]*, mirrored by blistering in *Perp*-null mouse stratified epithelia *[Mouse; PMID: 15797384, PMID: 16417219]*.
4. Loss of desmosomal adhesion / PERP function **results in epidermal hyperproliferation and altered differentiation**. *[Human + mouse]*
5. **Inferred:** downstream over-activation of **EGFR and mTOR/RPS6 signaling** in the epidermis drives hyperkeratosis. *[Human IHC; PMID: 31895414]*
6. This **produces the clinical palmoplantar and periorificial keratoderma with pain and pruritus**.

Branch (recessive): a **homozygous N-terminal truncation / biallelic missense** ablates or reduces PERP expression → loss of function → milder generalized erythrokeratoderma/ichthyosis with expansion of epidermal differentiation markers.



Supporting detail

> "Both exhibit epidermal hyperproliferation, immature desmosomes lacking a dense midline observed via electron microscopy, and impaired intercellular adhesion upon mechanical stress." — PMID: 30321533
>
> "Localization of other desmosomal components appears normal, which is in contrast to other conditions caused by mutations in genes encoding desmosomal proteins." — PMID: 30321533
>
> "increased phosphorylated ribosomal protein S6 (RPS6) and phosphorylated EGFR staining in the epidermis, indicating enhanced mTOR and EGFR signaling activation" — PMID: 31895414

- **Molecular pathways:** p63 → PERP transcriptional axis (upstream); desmosomal adhesion; downstream EGFR and mTOR/PI3K–AKT–RPS6 signaling (therapeutically targetable). Suggested GO: GO:0002934 (desmosome organization), GO:0007155 (cell adhesion), GO:0008544 (epidermis development), GO:0030216 (keratinocyte differentiation).
- **Cellular processes:** keratinocyte adhesion failure, epidermal hyperproliferation, abnormal keratinocyte differentiation. PERP is also p53/p63-linked to apoptosis.

- **Protein dysfunction:** dominant-negative (unstable truncated protein destabilizing desmosomes) vs loss of function (no expression).
- **Cell types:** keratinocytes of stratified squamous epithelium (CL:0000312 keratinocyte; CL:0000362 epidermal cell).
- **Upstream vs downstream:** the *PERP* desmosomal structural lesion is **upstream**; EGFR/mTOR activation and hyperkeratosis are **downstream** and druggable.

Molecular profiling is limited: lesional **immunohistochemistry** (p-RPS6, p-EGFR up) is the principal profiling data; no large transcriptomic/proteomic/metabolomic datasets specific to OLMS2 exist.

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7. Anatomical Structures Affected

- **Primary organ:** skin (UBERON:0002097), specifically palms and soles (palmoplantar epidermis) and periorificial skin (around mouth, eyes, nose, anus).
- **Secondary involvement:** hair (alopecia), nails, oral mucosa (leukokeratosis), cornea/eye (corneal defects). Body system: **integumentary system**.
- **Tissue/cell level:** stratified squamous **epithelium**; **keratinocytes** (CL:0000312) are the targeted cell population; desmosomes (cell–cell junctions) are the affected structure.
- **Subcellular level: desmosome** (GO:0030057, cellular component); plasma membrane. PERP is a tetraspan plasma-membrane/desmosomal protein.
- **Localization:** acral (palms/soles) and periorificial; **bilateral and symmetric**; transgredient (extending beyond palms/soles onto dorsal surfaces).

> "Perp localizes specifically to desmosomes, adhesion junctions important for tissue integrity" — PMID: 15797384

Suggested UBERON: UBERON:0002097 (skin of body), UBERON:0002389 (skin of manus/palm), UBERON:0001513 (skin of pes/sole), UBERON:0001456 (face skin / periorificial region).

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8. Temporal Development

- **Onset:** congenital / early childhood — PPK and periorificial plaques typically begin at birth or early childhood. Onset pattern is **chronic/insidious**.
- **Progression: progressive** — keratoderma worsens over time; pseudoainhum constricting bands can develop and progress toward a risk of autoamputation. Course is **chronic, lifelong**.
- **Disease duration:** lifelong; not self-limited.
- **Remission:** no spontaneous remission; partial, treatment-induced improvement reported with targeted therapy (erlotinib/sirolimus) and retinoids.
- **Critical periods:** early intervention may limit mutilating complications (pseudoainhum), but no formal natural-history window is defined.

> "...usually starting at birth or early childhood..." — PMID: 25886873

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9. Inheritance and Population

Epidemiology. Olmsted syndrome overall is ultra-rare — **~73 cases reported worldwide** by 2015 — with **male predominance**. PERP-related cases are a small subset first delineated in 2019. No validated prevalence/incidence rate exists.

> "About 73 cases have been reported worldwide. OS is observed in both sexes, although male cases are more frequent." — PMID: 25886873

Inheritance — dual pattern:

- **Autosomal dominant** OLMS2 from heterozygous C-terminal truncating variants, across multiple unrelated kindreds (de novo occurrence consistent with sporadic presentation).
- **Autosomal recessive** milder keratoderma/erythrokeratoderma from biallelic N-terminal truncating or missense variants, reported in **consanguineous families** (e.g., within a cohort of 180 extended Iranian families).

> "Heterozygosity for a C-terminal truncation...causes Olmsted syndrome with severe periorificial and palmoplantar keratoderma in multiple unrelated kindreds." — PMID: 30321533
>
> "Among 26 previously unresolved families within a cohort of 180 extended Iranian families with syndromic or non-syndromic ichthyosis" — PMID: 34863005

- **Penetrance:** high/complete for the dominant truncating variants (based on segregation in kindreds); expressivity varies with variant class (dominant-negative vs loss of function).
- **Genetic anticipation:** not applicable (not a repeat-expansion disorder).
- **Germline mosaicism:** not specifically documented.
- **Founder effects:** none established; variants are private/rare.
- **Consanguinity:** relevant to the recessive biallelic form (consanguineous Iranian families).
- **Carrier frequency:** not established; pathogenic alleles largely absent from gnomAD.
- **Sex ratio:** male predominance at the OS level.

Identifiers recap: MONDO:0030961 (OLMS2); ORPHA:659; *PERP* OMIM *609301; distinct from TRPV3-OS OMIM #614594.

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10. Diagnostics

Clinical diagnosis rests on the characteristic phenotype: bilateral mutilating transgredient PPK plus periorificial keratotic plaques (PMID: 25886873).

Skin biopsy / histopathology: epidermal hyperproliferation and hyperkeratosis; on **electron microscopy**, the hallmark finding is **immature desmosomes lacking a dense midline**, with normal localization of other desmosomal components.

> "immature desmosomes lacking a dense midline observed via electron microscopy" — PMID: 30321533

Immunohistochemistry (research/mechanistic): increased p-RPS6 and p-EGFR in lesional epidermis (PMID: 31895414).

Genetic testing (confirmatory): - **Whole-exome sequencing** or **NGS PPK/ichthyosis gene panels** including *PERP*, with Sanger confirmation. - **Homozygosity mapping** aids recessive-case resolution in consanguineous families (PMID: 34863005). - Single-gene *PERP* testing is appropriate when the phenotype is highly suggestive. WGS is useful but generally unnecessary. CMA/karyotype/FISH/mtDNA/repeat-expansion testing are **not applicable** (point-mutation single-gene disorder).

Differential diagnosis:

Condition	Gene	Distinguishing mechanism
TRPV3-Olmsted syndrome (OMIM #614594)	*TRPV3*	Gain-of-function cation channelopathy
MBTPS2-related X-linked Olmsted/IFAP/KFSD	*MBTPS2*	Membrane-bound protease; X-linked
Vohwinkel syndrome, Mal de Meleda, pachyonychia congenita	*GJB2/LOR*, *SLURP1*, keratins	Other mutilating/hereditary PPKs

> "Keratosis Follicularis Spinulosa Decalvans (KFSD), Olmsted syndrome, and Osteogenesis Imperfecta type XIX" — PMID: 33743732 (supporting MBTPS2 as a differential)

Screening: no newborn/population screening exists; **cascade genetic testing** of at-risk relatives and genetic counseling are appropriate once a familial variant is identified.

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11. Outcome / Prognosis

- **Survival / mortality:** OLMS2 is **non-lethal in humans**; life expectancy is not reduced by the skin disease itself. (By contrast, constitutive *Perp*-null mice die postnatally — a species difference reflecting gene dosage / complete loss.)
- **Morbidity / function:** high — mutilating PPK, pseudoainhum with autoamputation risk, severe pain and pruritus produce major, lifelong disability affecting mobility and manual function.
- **Quality of life:** substantially impaired; monitored via pain/pruritus VAS and CDLQI in therapy studies (PMID: 31895414).

- **Disease course:** chronic, progressive; complications include secondary infection of fissured keratotic skin, constricting bands, and functional loss.
- **Recovery potential:** no cure; partial improvement with targeted therapy and supportive care.
- **Prognostic factors:** variant class (dominant-negative C-terminal truncation = most severe), extent of pseudoainhum, and response to EGFR/mTOR-targeted therapy.

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12. Treatment

There is **no approved disease-specific therapy**. Management is multimodal.

Targeted pharmacotherapy (emerging, mechanism-based):

Drug	Class / target	Dose (reported)	Evidence	NCIT suggestion
Erlotinib	EGFR tyrosine-kinase inhibitor	2 mg/kg/d	Efficacy in OS incl. TRPV3-OS; mechanism via ↓EGFR signaling	NCIT:C65530 (Erlotinib)
Sirolimus	mTOR inhibitor	0.8 mg/m² BID, trough 10–15 ng/mL	Used in 4 refractory OS children	NCIT:C1212 (Sirolimus)

> "Lesional skin immunostaining showed increased phosphorylated ribosomal protein S6 (RPS6) and phosphorylated EGFR staining in the epidermis, indicating enhanced mTOR and EGFR signaling activation." — PMID: 31895414
>
> "A review of the literature indicates that erlotinib has shown efficacy in other cases of OS, making it a promising therapeutic option." — PMID: 39910762

Note: the strongest published erlotinib data are in **TRPV3**-associated OS (PMID: 39926429, PMID: 39910762); extrapolation to *PERP*-OLMS2 is rational given shared downstream EGFR/mTOR activation but remains to be demonstrated specifically for *PERP* cases.

Conventional / supportive therapy (NCIT suggestions in parentheses): - Oral retinoids — **acitretin** (NCIT:C1878, Acitretin). - Topical keratolytics and emollients (NCIT:C1507, Keratolytic Agent). - Pain and pruritus management. - **Surgical release** of constricting pseudoainhum bands to prevent autoamputation; wound care.

Pharmacogenomics / cell / gene / RNA therapies: none established; no approved advanced therapeutics for OLMS2.

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13. Prevention

- **Primary prevention:** not possible (Mendelian germline disorder). **Genetic counseling** is the mainstay — risk assessment and family-planning guidance for affected families.
- **Secondary prevention:** early diagnosis and early targeted/supportive therapy to limit mutilating complications.
- **Tertiary prevention:** managing pseudoainhum, treating secondary infections, preserving function.
- **Genetic screening:** cascade testing of relatives; prenatal testing / preimplantation genetic diagnosis are feasible once the familial *PERP* variant is known.
- **Immunization / public health / environmental interventions:** not applicable.

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14. Other Species / Natural Disease

- **Orthologous gene:** mouse *Perp* (well characterized; see Section 15). Human *PERP* NCBI Gene 64065.
- **Natural disease in other species:** no naturally occurring *PERP*-related Olmsted-like disease documented in companion animals or wildlife (OMIA); the animal evidence is from engineered models.
- **Comparative biology:** *Perp* function in desmosomal adhesion and epithelial integrity is **evolutionarily conserved** between mouse and human; the human dominant disease arises via a dominant-negative truncation, whereas complete murine loss is postnatally lethal — a dosage/species difference.
- **Transmission / zoonosis:** not applicable (non-infectious genetic disease).

15. Model Organisms

Mouse (*Mus musculus*) is the principal model.

Model	Phenotype	Recapitulation	PMID
Constitutive *Perp*-null	Postnatal lethality; dramatic blistering in stratified epithelia; numerous desmosomal defects	Captures adhesion failure & desmosomal pathology; more severe (lethal) than human	15797384
Epithelium-specific K5-Cre conditional *Perp* KO	Postnatal lethality, blistering, hyperproliferation	Confirms cell-intrinsic role in stratified epithelia	16417219
Perp-loss + UVB	Promotes cutaneous squamous cell carcinoma initiation & progression	Reveals tumor-suppressor function (p53/p63-regulated)	20975948

> "Perp-/- mice die postnatally, with dramatic blistering in stratified epithelia symptomatic of compromised adhesion." — PMID: 15797384
>
> "the majority of mice lacking Perp in stratified epithelia die within 10 days after birth, accompanied by blistering and hyperproliferation in the epithelia" — PMID: 16417219
>
> "Perp ablation promotes both tumor initiation and progression" — PMID: 20975948

Model characteristics. These knockout/conditional-knockout models strongly recapitulate the desmosomal adhesion defect, blistering, and epidermal hyperproliferation of human disease, and established PERP as a p63 target. **Limitation:** complete murine loss is postnatally lethal and models the *recessive loss-of-function* end of the spectrum, not the human *dominant-negative* OLMS2 mechanism; a knock-in mouse carrying a human C-terminal truncation would better model dominant OLMS2. **Resources:** MGI (mouse *Perp*). No published zebrafish/*Drosophila*/organoid OLMS2 models were identified; patient-derived keratinocytes / iPSC-organoids are a logical but not-yet-reported avenue.

An incidental *PERP* missense variant (p.Gly59Arg) was found in an ARVC screen but was of uncertain significance (PMID: 23858024), reflecting *PERP* expression in heart; this is not OLMS2.

Mechanistic Model / Interpretation

OLMS2 is best understood as a **desmosomal adhesion disease with a druggable downstream amplifier**. The primary lesion is structural — a *PERP* truncation that either destabilizes desmosomes (dominant-negative, C-terminal) or eliminates PERP (loss of function, N-terminal/missense). Because PERP is a p63 target essential for stratified-epithelial integrity, its disruption causes immature desmosomes and keratinocyte adhesion failure under the mechanical stress that acral and periorificial skin routinely experience. The epidermis responds with hyperproliferation and abnormal differentiation, and lesional tissue shows upregulated EGFR and mTOR/RPS6 signaling. This downstream node — not the structural defect — is what current targeted therapies (erlotinib, sirolimus) engage, which explains why they can ameliorate keratoderma, pain, and pruritus without correcting the underlying desmosomal lesion.

The clean genotype–phenotype gradient (dominant-negative truncation → severe OLMS2; loss of function → milder erythrokeratoderma) is the most distinctive feature of this disease and the single most useful fact for clinical interpretation of a newly discovered *PERP* variant.

Evidence Base

PMID	Title (abbrev.)	Role in this report
30321533	*Mutations in PERP Cause Dominant and Recessive Keratoderma*	**Landmark** — defines OLMS2; dominant-negative vs LoF mechanisms; EM desmosomal immaturity
34863005	*Ichthyosis...biallelic mutations in PERP*	Recessive variant spectrum; exact nomenclature; consanguineous cohort
25886873	*Olmsted syndrome: clinical, molecular and therapeutic aspects*	Phenotype definition, epidemiology (~73 cases), sex ratio, differential dx
31895414	*Targeted inhibition of EGFR and mTOR in Olmsted syndrome*	Downstream EGFR/mTOR activation; erlotinib + sirolimus rationale
15797384	*Perp is a p63-regulated gene essential for epithelial integrity*	p63→PERP axis; desmosomal localization; null-mouse phenotype
16417219	*Perp requirement in postnatal viability / epithelial integrity*	Conditional KO confirms cell-intrinsic role
20975948	*Loss of Perp promotes tumorigenesis*	Tumor-suppressor function (UVB SCC)
33743732	*MBTPS2...skin and bone disorders*	Supports MBTPS2-OS differential
39910762 / 39926429	*Erlotinib in TRPV3-OS*	Erlotinib efficacy (TRPV3-OS context)
21965674	*SATB2 and p63 mutant proteins*	p63/SATB2 regulation of *perp*
23858024	*Junctional candidates in ARVC*	Incidental PERP variant (not OLMS2)

Evidence source types: human clinical/genetic (30321533, 34863005, 25886873, 31895414); model organism (15797384, 16417219, 20975948); in vitro/IHC (30321533, 31895414).

Limitations and Knowledge Gaps

1. **Ultra-rarity.** The entire *PERP*-OLMS2 literature rests on a small number of kindreds; no prevalence/incidence, formal penetrance estimates, or natural-history cohorts exist.
2. **Downstream mechanism is inferred.** EGFR/mTOR activation is demonstrated by lesional IHC in Olmsted syndrome, but the causal link from desmosomal failure to EGFR/mTOR activation is not mechanistically proven, and the IHC evidence is not exclusively from *PERP* cases.
3. **Therapy evidence is indirect for PERP.** The best erlotinib/sirolimus data come from *TRPV3*-OS; direct *PERP*-OLMS2 treatment-response data are minimal.
4. **No dominant-negative animal model.** Mouse models reproduce loss of function (lethal), not the human dominant-negative OLMS2 mechanism.
5. **No omics depth.** No transcriptomic/proteomic/metabolomic/single-cell datasets specific to OLMS2; molecular profiling is limited to IHC.
6. **Variant classification.** Few variants, no ClinVar-scale curation, and no functional assays for most missense variants.

Proposed Follow-up Experiments / Actions

1. **Knock-in dominant-negative mouse or human keratinocyte/organoid model** expressing a C-terminal truncated *PERP* to directly test the dominant-negative desmosome-destabilization mechanism and recapitulate OLMS2 (rather than lethal loss of function).
2. **Mechanistic linkage study:** test whether restoring desmosomal adhesion or depleting mutant PERP normalizes EGFR/mTOR–RPS6 signaling in patient-derived keratinocytes — to prove the inferred downstream step.
3. **Prospective, *PERP*-specific therapeutic registry/trial** of erlotinib and/or sirolimus with standardized VAS/CDLQI endpoints and lesional p-EGFR/p-RPS6 as pharmacodynamic biomarkers.
4. **Functional classification of *PERP* VUS** (e.g., recessive missense p.Leu30Pro, p.Gly156Arg) via desmosome-incorporation and adhesion assays to support ACMG curation.
5. **International OLMS2 registry** to estimate prevalence, penetrance, expressivity, and natural history, and to collect ultrastructural EM data as a diagnostic standard.

6. **Single-cell/spatial transcriptomics of lesional skin** to map keratinocyte-state changes and signaling activation in situ.

Report compiled from 9 confirmed findings and 20 reviewed papers over a 5-iteration autonomous investigation. Evidence quotes are verbatim from the cited abstracts.
