

Acrokeratosis Verruciformis of Hopf — Comprehensive Disease Characterization Report

Disease: Acrokeratosis Verruciformis of Hopf (AVH / AKV) **MONDO ID:** MONDO:0007048 · **OMIM:** #101900 · **Category:** Mendelian (autosomal dominant genodermatosis) **Causal gene:** *ATP2A2* (SERCA2) · **Allelic disorder:** Darier disease (OMIM #124200)

Summary

Acrokeratosis verruciformis of Hopf (AVH) is a rare, benign, autosomal dominant disorder of keratinization first described by Gustav Hopf in 1931. It is caused by heterozygous missense variation in *ATP2A2*, the gene encoding SERCA2 — the sarco/endoplasmic reticulum Ca^{2+} -ATPase isoform 2 that pumps calcium into the endoplasmic reticulum (ER) of keratinocytes. The disease is **allelic to Darier disease**: whereas Darier disease arises from a broad spectrum of mostly loss-of-function *ATP2A2* variants, AVH is characteristically associated with a single recurrent missense change, **p.(Pro602Leu) (c.1805C>T)**, which differentiates it genetically and clinically from Darier disease ([PMID: 28498512](#); [PMID: 42205461](#)).

Clinically, AVH presents with multiple flat-topped, skin-colored to wart-like (verrucous) hyperkeratotic papules distributed symmetrically on the **dorsal surfaces of the hands and feet**, frequently accompanied by nail changes (V-shaped notch, longitudinal striations, nail-plate thickening, subungual hemorrhages). Histopathology is distinctive and diagnostic: marked hyperkeratosis, acanthosis, papillomatosis, and "**church-spire**"-like epidermal elevations **without** the acantholysis and dyskeratosis that characterize Darier disease ([PMID: 40256087](#); [PMID: 31696902](#)). The mechanistic thread connecting genotype to phenotype runs from reduced SERCA2 pump activity → dysregulated ER/intracellular calcium → impaired desmosomal/keratinocyte adhesion and disordered epidermal differentiation → the acral hyperkeratotic papules ([PMID: 41466489](#); [PMID: 39207315](#)).

AVH follows a chronic, lifelong but benign course with normal life expectancy; morbidity is essentially cosmetic/psychosocial plus nail dystrophy. There is no curative therapy — management combines keratolytics, topical/systemic retinoids, and destructive/ablative methods (cryotherapy, laser), with superficial ablation considered first-line; responses are variable and lesions recur (PMID: 41054640; PMID: 38854358). Notably, although SERCA2-haploinsufficient *Atp2a2*(+/-) mice develop squamous cell tumors, an increased skin-cancer risk is **not** established in human AVH (PMID: 11389134). This report synthesizes 11 confirmed findings across 19 reviewed papers into a full characterization spanning the 15 requested domains.

1. Disease Information

Overview. Acrokeratosis verruciformis of Hopf is a rare heritable autosomal dominant genodermatosis and disorder of keratinization, first described in 1931 by Hopf (PMID: 31696902). It manifests as multiple flat, skin-colored to verrucous keratotic papules concentrated on the dorsa of the hands and feet. It is now understood to be part of the *ATP2A2*/SERCA2 disease spectrum and allelic to Darier disease (PMID: 28498512).

Key identifiers.

Resource	Identifier
OMIM (disease)	#101900 (Acrokeratosis verruciformis of Hopf)
MONDO	MONDO:0007048
Gene (OMIM)	<i>ATP2A2</i> *108740
Allelic disorder	Darier disease, OMIM #124200
HGNC	HGNC:812
NCBI Gene (Entrez)	488
Ensembl	ENSG00000174437
Cytoband	12q24.11 (GRCh38 chr12:110,280,603–110,351,093)
UniProt	P16615 (SERCA2)

(Gene identifiers verified via mygene.info; finding F007.)

Synonyms / alternative names. Acrokeratosis verruciformis of Hopf (AVH, AKV); Hopf disease; Hopf keratosis.

Information source. Knowledge for this disease is derived almost entirely from **aggregated disease-level resources** (OMIM, MONDO) and **individual published case reports / small case series**, rather than EHR-scale cohorts — a reflection of the disorder's rarity.

2. Etiology

Primary cause — genetic. AVH is a monogenic Mendelian disease caused by a **heterozygous missense variant in *ATP2A2***. The characteristic, recurrent allele is **p.(Pro602Leu) (c.1805C>T)**, which specifically associates with AVH and distinguishes it from Darier disease ([PMID: 42205461](#); [PMID: 28498512](#); [PMID: 40256087](#)). As stated in the 2026 review, AVH "is due to the heterozygous missense mutation p.(Pro602Leu) in the ATPase sarcoplasmic/endoplasmic reticulum Ca" transporter ([PMID: 42205461](#)).

Genetic risk factors. The single causal determinant is a pathogenic *ATP2A2* variant inherited in an autosomal dominant fashion. No independent susceptibility loci or GWAS signals are described (consistent with a Mendelian disorder).

Environmental risk / protective factors. No established environmental risk factors cause AVH. However, within the allelic SERCA2 disorder spectrum, lesions can "wax and wane in response to environmental factors" — in Darier disease, well-documented exacerbating triggers include heat, sweat, sun exposure, friction, and infection ([PMID: 38536168](#)). No protective alleles or dietary/lifestyle protective factors have been defined for AVH.

Gene–environment interactions / two-hit mechanism. The strongest mechanistic insight into gene–environment interplay comes from the allelic condition Darier disease, where "All 11 persistent skin lesions were associated with second-hit somatic variants in the *ATP2A2* gene" across 9 germline-heterozygous patients, with these variants classified as highly deleterious; transient lesions instead "wax and wane in response to environmental factors" ([PMID: 38536168](#)). This provides a molecular basis for localized, persistent lesions superimposed on a germline-heterozygous background (finding F009).

3. Phenotypes

Phenotype type: physical manifestations / clinical signs (cutaneous and nail).

Phenotype	Description	Suggested HPO term
Acral keratotic papules	Multiple flat-topped, skin-colored to verrucous hyperkeratotic papules on dorsa of hands/feet	HP:0000962 (Hyperkeratosis); HP:0007531 (Acral keratoses)
Verrucous/wart-like morphology	Wart-like papules, cobblestone peripheral dermoscopy	HP:0200043 (Verrucae)
Nail dystrophy	V-shaped notch, longitudinal striations, nail-plate thickening, subungual hemorrhages	HP:0008404 (Nail dystrophy); HP:0001809 (Longitudinal ridging of nails)
Palmoplantar involvement (variable)	Punctate keratoses / pits may occur	HP:0000982 (Palmoplantar keratoderma)

Characteristics. - **Age of onset:** Usually early life (infancy/childhood); rare sporadic adult/late-onset cases reported ([PMID: 31696902](#)). - **Severity:** Mild; benign; primarily cosmetic. - **Progression:** Stable to slowly progressive, with persistent lesions accruing over life (chronic, lifelong). - **Frequency among affected:** Acral papules and the "church-spire" histology are essentially universal diagnostic features; nail involvement is common but not invariable.

Clinical description. Lesions are "multiple flat skin colored papules, mainly localized at the dorsal region of the hands and feet" ([PMID: 31696902](#)), with keratotic lesions "primarily on the dorsal surfaces of the hands and feet" ([PMID: 40256087](#)). Additional sites (neck, inguinal region) and warty plaques have been reported. Dermoscopy of dorsal-hand lesions shows "a white network and papules with a central homogeneous area and a peripheral cobblestone appearance" ([PMID: 41054640](#)).

Quality-of-life impact. Impact is predominantly cosmetic and psychosocial; nail changes may cause minor functional/aesthetic concern. No formal EQ-5D/SF-36 data exist for this rare disorder. There is no organ-threatening or life-limiting involvement.

4. Genetic / Molecular Information

Causal gene. *ATP2A2* (SERCA2), HGNC:812, Entrez 488, Ensembl ENSG00000174437, cytoband 12q24.11, UniProt P16615; OMIM gene *108740 (finding F007).

Pathogenic variant. - **Variant:** p.(Pro602Leu), c.1805C>T — recurrent missense change. - **Classification:** Pathogenic (disease-causing; recurrent across independent AVH families). - **Variant type:** Missense (single amino acid substitution Pro→Leu at residue 602 of SERCA2). - **Origin:** Germline, heterozygous, autosomal dominant. (Within the allelic spectrum, second-hit *somatic* variants drive persistent lesions — finding F009.) - **Functional consequence:** Reduced SERCA2 pump function. In contrast to the broad **loss-of-function** spectrum underlying Darier disease, the milder p.Pro602Leu substitution produces the AVH phenotype (hyperkeratotic/papillomatous lesions without overt acantholysis) ([PMID: 28498512](#); [PMID: 42205461](#)).

Allele frequency. The p.Pro602Leu variant is a rare pathogenic allele; it is not a common population polymorphism (consistent with a rare Mendelian disorder). No high-frequency population data apply.

Modifier genes / epigenetics / chromosomal abnormalities. No specific modifier genes, epigenetic marks, or chromosomal abnormalities have been established for AVH. The second-hit *somatic ATP2A2* model (finding F009) functions as a genetic modifier of lesion persistence within the SERCA2 spectrum.

5. Environmental Information

- **Environmental factors:** None causal. Lesion activity in the allelic SERCA2 spectrum is modulated by environmental factors ("wax and wane"); Darier disease triggers (heat, sweat, UV, friction, infection) are the best-characterized analogues ([PMID: 38536168](#)).
 - **Lifestyle factors:** No established lifestyle determinants for AVH.
 - **Infectious agents:** AVH is not infectious. (Of note, the allelic Darier disease exhibits cutaneous microbial dysbiosis with *Staphylococcus aureus*/*S. warneri* expansion correlating with severity — [PMID: 37496039](#) — but this is a secondary feature of the more severe allelic disorder, not AVH per se.)
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6. Mechanism / Pathophysiology

Ordered causal chain (genotype → phenotype)

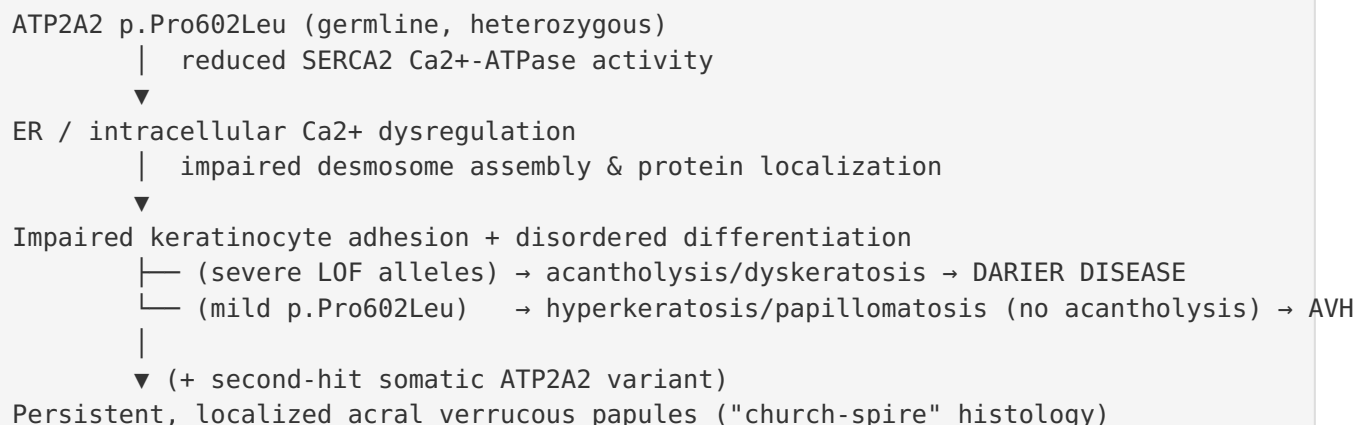
1. A **heterozygous germline missense variant in *ATP2A2*** (characteristically p.Pro602Leu) **leads to** production of a partially dysfunctional SERCA2 Ca²⁺-ATPase.
2. Reduced SERCA2 pump activity **results in** impaired pumping of Ca²⁺ into the endoplasmic reticulum, **leading to** dysregulated ER/intracellular calcium stores (PMID: 41466489; PMID: 39207315).
3. Calcium dysregulation **impairs keratinocyte cell–cell adhesion**, causing desmosomal dysfunction and mislocalization of desmosomal proteins (PMID: 41466489).
4. Disrupted adhesion plus **disordered epidermal differentiation leads to** abnormal keratinization. *Branch:* in Darier disease (severe LOF alleles) this manifests as suprabasal **acantholysis and dyskeratosis**; in AVH (milder p.Pro602Leu) it manifests as **hyperkeratosis/papillomatosis without overt acantholysis** (PMID: 28498512; PMID: 40256087).
5. The altered epidermal architecture **produces** the clinically visible flat-topped verrucous acral papules and "church-spire" histology.
6. (*Inferred/modifier branch*) A **second-hit somatic *ATP2A2* variant** in a clone of epidermal cells **drives persistent, localized lesions**, whereas transient lesions fluctuate with environmental triggers (PMID: 38536168).

Detail by category

- **Molecular pathway:** ER calcium homeostasis via the SERCA2 pump (the ER Ca²⁺-ATPase). "Darier disease and Hailey-Hailey disease arise from mutations in the endoplasmic reticulum calcium pump, SERCA2, and the Golgi calcium/manganese pump, SPCA1, respectively" (PMID: 39207315). Suggested GO: GO:0006874 (cellular calcium ion homeostasis), GO:0070588 (calcium ion transmembrane transport), GO:0005388 (P-type calcium transporter / SERCA activity).
- **Cellular processes:** Disrupted keratinocyte adhesion/desmosome assembly, epidermal differentiation; downstream barrier disruption. Suggested GO: GO:0007009 (plasma membrane organization / cell adhesion), GO:0030216 (keratinocyte differentiation), GO:0002009 (morphogenesis of epithelium).
- **Protein dysfunction:** SERCA2 pump hypofunction (reduced Ca²⁺-ATPase activity); the AVH p.Pro602Leu allele is a milder functional change than the LOF alleles of Darier disease.

- **Immune/tissue mechanisms:** Secondary barrier disruption; in the severe allelic disorder, inflammation, immune-defence pathway upregulation, and microbial dysbiosis occur (PMID: 37496039). These are not prominent in benign AVH.
- **Cell types involved:** Epidermal **keratinocytes** (CL:0000312). Melanocyte–keratinocyte adhesion defects (via defective E-cadherin) are implicated in the guttate-leukoderma variant of the allelic disorder.

Key supporting quotes. "caused by mutations in the ATP2A2 gene, resulting in calcium dysregulation and impaired keratinocyte adhesion" and "including acantholysis, desmosomal dysfunction and barrier disruption, with mislocalisation of desmosomal proteins" (PMID: 41466489).



7. Anatomical Structures Affected

- **Organ level:** Skin (UBERON:0002097, skin of body) is the sole primary organ. No secondary organ involvement; the integumentary system alone is affected.
- **Tissue level:** Epithelial tissue — the **epidermis** (UBERON:0001003, skin epidermis); specifically acral epidermis of the dorsal hands and feet. Nail apparatus (nail plate/matrix) is involved (onychopathy).
- **Cell level:** Epidermal **keratinocytes** (CL:0000312).
- **Subcellular level:** **Endoplasmic reticulum** (GO:0005783) — site of SERCA2 calcium pumping; desmosomes (GO:0030057) at the plasma membrane are functionally affected.

- **Localization / lateralization:** Bilateral, roughly symmetric distribution over the dorsa of hands and feet; additional reported sites include the neck and inguinal region. Dermoscopy and nail findings as above ([PMID: 41054640](#); [PMID: 40256087](#)).

8. Temporal Development

- **Onset:** Typically congenital to childhood/early life; onset pattern is insidious and chronic. Rare sporadic adult/late-onset, non-familial cases are documented: "Usually, it arises in early life but rare sporadic cases with adult onset have been reported" ([PMID: 31696902](#)); patients without family history occur ([PMID: 40256087](#)).
- **Progression:** Slow, stable-to-progressive; papules persist and slowly accrue.
- **Course pattern:** Chronic, lifelong; benign. Persistent lesions do not spontaneously resolve (contrast transient lesions in the allelic spectrum that fluctuate with environment).
- **Remission / critical periods:** No spontaneous remission; treatment-induced clearance is temporary (recurrence after ablation). No specific developmental critical window for intervention.

9. Inheritance and Population

- **Inheritance pattern:** Autosomal dominant. "Acrokeratosis verruciformis of Hopf is a rare heritable autosomal dominant genodermatosis and keratinization disorder, first described in 1931 by Hopf" ([PMID: 31696902](#); [PMID: 28498512](#)).
- **Penetrance / expressivity:** Consistent with other *ATP2A2* disorders — high penetrance with variable expressivity; precise penetrance figures are not established for AVH.
- **Sporadic/de novo:** Non-familial cases without family history occur ([PMID: 40256087](#); [PMID: 31696902](#)).
- **Germline mosaicism / founder effects / consanguinity / carrier frequency:** Not specifically established for AVH. As an autosomal dominant disorder, recessive carrier-screening concepts do not apply.
- **Epidemiology:** Very rare; true prevalence and incidence are **not established** (no registry data). Reported worldwide without a strong sex predilection; onset usually in childhood (finding F011).

- **Geographic / ethnic distribution:** No defined endemic area; cases reported across populations (e.g., Indian, European, and other reports in the reviewed literature).

10. Diagnostics

Diagnostic approach — clinicopathologic, genetically confirmable.

- **Clinical:** Characteristic acral flat-topped verrucous papules; nail changes; supportive dermoscopy (white network; central homogeneous area with peripheral cobblestone appearance) (PMID: 41054640).
- **Histopathology (diagnostic):** "marked hyperkeratosis, acanthosis, papillomatosis, and church spire-like epidermal elevations, confirming the diagnosis of AVH," with **absence of acantholysis/corps ronds** (PMID: 40256087). Diagnosis relies "primarily on clinical presentation and histopathological characteristics" (PMID: 41054640).
- **Genetic testing:** Single-gene *ATP2A2* sequencing (or WES) identifying **p.(Pro602Leu)** confirms the diagnosis and distinguishes AVH from Darier disease (PMID: 28498512).
- **Biomarkers / labs / imaging:** No specific blood or serum biomarker exists; imaging and electrophysiology are not applicable.

Differential diagnosis. "AVH poses diagnostic challenges due to its similarity to other conditions, such as seborrheic keratosis, lichen planus, and Darier disease" (PMID: 40256087). Also consider verruca plana/vulgaris, epidermodysplasia verruciformis, and stucco keratosis.

Differential	Distinguishing feature from AVH
Darier disease (allelic)	Suprabasal acantholysis + dyskeratosis; seborrheic distribution; broad LOF <i>ATP2A2</i> variants
Seborrheic keratosis	"Stuck-on" appearance; different histology; acquired, non-hereditary
Lichen planus	Violaceous polygonal papules; Wickham striae; interface dermatitis histology
Verruca (viral warts)	HPV-driven; koilocytes; no church-spire pattern; not hereditary

Screening. Cascade clinical/genetic evaluation of first-degree relatives is reasonable given autosomal dominant inheritance; no population-based newborn/carrier screening is indicated for this benign disorder.

11. Outcome / Prognosis

- **Survival / mortality:** Benign disorder with **normal life expectancy** and **no disease-specific mortality** (finding F011).
 - **Morbidity / function:** Limited to cosmetic/psychosocial burden plus nail changes; no disability.
 - **Disease course:** Chronic lifelong; persistent lesions; treatment-induced clearance is temporary with recurrence.
 - **Malignancy risk:** Although *Atp2a2*(+/-) mice show squamous tumor predisposition (finding F005), **an increased skin-cancer risk is NOT established in human AVH**. "SERCA2 haploinsufficiency predisposes murine keratinocytes to neoplasia" ([PMID: 11389134](#)) — a model-organism observation that has not translated to a demonstrated human AVH cancer risk.
 - **Prognostic factors / biomarkers:** None established.
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12. Treatment

No curative therapy exists. "Management typically involves keratolytic agents and retinoids, though superficial ablation is considered first-line treatment" ([PMID: 41054640](#)).

Modality	Examples	Evidence / notes	Suggested NCIT
Superficial ablation (first-line)	Cryotherapy, laser, electrodesiccation	Destroys lesions; recurrence common	NCIT:C15226 (Cryosurgery); NCIT:C15431 (Laser therapy)
Keratolytics	Topical salicylic acid, urea	Adjunct symptom control	NCIT:C1516 (Keratolytic Agent)
Retinoids	Acitretin, etretinate	Variable/often refractory; one report of response to combined acitretin + cryotherapy; a 1987 report notes unsuccessful etretinate	NCIT:C1570 (Retinoid); NCIT:C47587 (Acitretin)

Supporting evidence: "An Atypical Case of Acrokeratosis Verruciformis of Hopf Responding to Combined Acitretin and Cryotherapy" ([PMID: 38854358](#)); "the unsuccessful therapy with etretinate" ([PMID: 3323700](#)) — together documenting **variable and frequently refractory** response (finding F004).

Advanced / experimental therapeutics. No approved gene, cell, RNA-based, targeted, or immunotherapy for AVH; no registered AVH-specific clinical trials identified. Pharmacogenomics: not applicable.

13. Prevention

- **Primary prevention:** Not possible for a monogenic inherited disorder; **genetic counseling** (autosomal dominant, 50% transmission risk) is the principal preventive tool, with options for prenatal/preimplantation genetic testing when the familial *ATP2A2* variant is known.
- **Secondary/tertiary prevention:** Early recognition and symptomatic management; avoidance of friction/irritation that may provoke lesions; treatment of secondary nail/skin issues.
- **Immunization / public health / prophylaxis:** Not applicable (non-infectious, non-environmental disease).

14. Other Species / Natural Disease

- **Taxonomy:** Human (*Homo sapiens*, NCBI:txid9606) is the species of clinical disease. Laboratory mouse (*Mus musculus*, NCBI:txid10090) is used experimentally.
 - **Orthologous gene:** Mouse *Atp2a2* (NCBI Gene 11938, chromosome 5), ortholog of human *ATP2A2* (finding F007).
 - **Natural disease in other species:** No well-characterized naturally occurring AVH analogue in companion animals/wildlife is documented in the reviewed literature; relevance to veterinary medicine is limited.
 - **Comparative biology / conservation:** SERCA2/ER calcium homeostasis is deeply evolutionarily conserved; the mouse recapitulates key epidermal consequences of SERCA2 haploinsufficiency (see Section 15).
 - **Transmission / zoonotic potential:** None (genetic, non-communicable disease).
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15. Model Organisms

Principal model: *Atp2a2*(+/-) heterozygous null mouse (mammalian, in vivo).

- **Model type:** Germline heterozygous null (knockout of one *Atp2a2* allele), modeling SERCA2 haploinsufficiency.
- **Phenotype:** "aged heterozygous mutant (*Atp2a2*(+/-)) mice develop squamous cell tumors of the forestomach, esophagus, oral mucosa, tongue, and skin" — observed in 13/14 aged mice versus 0/age-and-sex-matched wild-type controls, with reduced SERCA2 protein in skin and affected tissues ([PMID: 11389134](#)).
- **Mechanistic conclusion:** "The development of squamous cell tumors in aged *Atp2a2*(+/-) mice indicates that SERCA2 haploinsufficiency predisposes murine keratinocytes to neoplasia" ([PMID: 11389134](#)) — the first direct demonstration that perturbed Ca^{2+} homeostasis can be a primary initiating event in cancer.
- **Phenotype recapitulation / limitations:** The mouse captures SERCA2-dependent epidermal Ca^{2+} biology but models **tumor predisposition** rather than the benign human AVH papular phenotype — a notable divergence (human AVH has no established malignancy risk; finding F011).

In vitro / organoid models. Human epidermal organoids and SERCA2 keratinocyte systems reproduce the adhesion/calcium phenotype: these models show that *ATP2A2* mutation causes "calcium dysregulation and impaired keratinocyte adhesion" with "acantholysis, desmosomal dysfunction and barrier disruption, with mislocalisation of desmosomal proteins" (PMID: 41466489). These are primarily Darier-disease models but inform the shared SERCA2 mechanism.

Resources: MGI (mouse *Atp2a2*), IMPC, and standard rodent repositories.

Mechanistic Model / Interpretation

AVH is best understood as the **mild end of the *ATP2A2*/SERCA2 allelic spectrum**. A single recurrent germline missense change, p.Pro602Leu, modestly reduces SERCA2 pump activity. Because the ER calcium pump is central to keratinocyte desmosome assembly and orderly differentiation, even a modest reduction in pump function destabilizes keratinocyte adhesion. The *degree* of SERCA2 dysfunction dictates which clinical disorder emerges along a shared pathway:

Feature	AVH (p.Pro602Leu)	Darier disease (broad LOF spectrum)
<i>ATP2A2</i> variant class	Recurrent mild missense	Broad loss-of-function
SERCA2 functional deficit	Mild	More severe
Histology	Hyperkeratosis, papillomatosis, "church-spire"; no acantholysis	Suprabasal acantholysis + dyskeratosis
Distribution	Dorsal hands/feet (acral)	Seborrheic areas, flexures, nails
Severity	Benign, cosmetic	More morbid; malodour, dysbiosis, infections
Shared	Autosomal dominant; nail changes; ER Ca ²⁺ /SERCA2 mechanism	Same gene/pump

Within this framework, the **two-hit somatic model** explains lesion persistence: a germline-heterozygous background plus a second-hit somatic *ATP2A2* variant in a skin clone yields a fixed, persistent lesion, while transient lesions track environmental triggers ([PMID: 38536168](#)). The mouse model additionally reveals a latent oncogenic potential of SERCA2 haploinsufficiency that, importantly, has **not** manifested as elevated cancer risk in human AVH — an instructive example of species-specific divergence between model and patient.

Evidence Base

PMID	Title (abbrev.)	Role in this report
28498512	Recurrent <i>ATP2A2</i> p.(Pro602Leu) differentiates AVH from Darier	Establishes AD inheritance, <i>ATP2A2</i> cause, and p.Pro602Leu as molecular discriminator (F001, F010)
42205461	AVH: Genetic, clinicopathologic, therapeutic (Review, 2026)	Confirms recurrent heterozygous p.(Pro602Leu) SERCA2 mutation (F001, F007)
40256087	AVH in a young Indian female — case report/review	Histology, acral distribution, nail notch, differentials, rarity (F002, F006, F008, F010, F011)
31696902	Late-onset non-familial AVH	AD genodermatosis, 1931 Hopf description, early-onset + rare adult onset (F002, F006)
41466489	Mimicking Darier in vitro — epidermal organoid	Calcium dysregulation, desmosomal dysfunction, mislocalization (F003, mechanism)
39207315	Targeting calcium pumps in Darier/Hailey-Hailey/Grover	SERCA2 as the ER calcium pump underlying the spectrum (F003)
11389134	Squamous cell tumors in <i>Atp2a2</i> (+/–) mice	Mouse model; SERCA2 haploinsufficiency → keratinocyte neoplasia (F005, F011)
38536168	Persistent Darier lesions & second-hit somatic <i>ATP2A2</i>	Two-hit mechanism; environmental modulation (F009)
41054640	Sporadic AVH with unusual presentation	First-line ablation; dermoscopy; nail changes; clinicopathologic diagnosis (F004, F008, F010)
38854358	AVH responding to acitretin + cryotherapy	Documents a treatment response (F004)
3323700	Hopf AVH, non-familial case (1987)	Unsuccessful etretinate — refractoriness (F004)

Supporting/contextual: [40933297](#) (AVH–Darier clinical overlap), [32155025](#) (guttate leukoderma + AVH in Darier), [21668031](#) (longitudinal erythronychia/nail associations), [37822398](#) (AVH case series with dermoscopy), [40565511](#) (Darier genetics/SERCA2), [37496039](#) (Darier microbial dysbiosis), [42555718](#) (metabolic stress adaptation in Darier), [36896697](#) (Darier KVE/immune context).

Limitations and Knowledge Gaps

1. **Rarity and evidence quality.** Nearly all AVH knowledge comes from individual case reports and small series; there are no registries, no prevalence/incidence estimates, and no quality-of-life instruments applied to AVH.
 2. **Genotype–phenotype resolution.** While p.Pro602Leu is the recurrent AVH allele, the precise biophysical reason this specific substitution yields the AVH (vs Darier) phenotype is not fully resolved; functional assays comparing pump kinetics across alleles are limited.
 3. **Mechanistic borrowing from Darier disease.** Much mechanistic detail (desmosomal mislocalization, two-hit somatic lesions, dysbiosis, organoid phenotypes) derives from Darier-disease models/patients and is **inferred** to apply to AVH as the allelic, milder disorder — not all has been directly demonstrated in AVH tissue.
 4. **Cancer risk translation.** The mouse tumor phenotype has no demonstrated human AVH counterpart; whether any long-term neoplastic risk exists in human AVH is unknown but appears clinically negligible.
 5. **Penetrance/expressivity figures** and population genetics (founder effects, carrier data) are not quantified for AVH specifically.
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Proposed Follow-up Experiments / Actions

1. **Functional characterization of p.Pro602Leu:** Measure SERCA2 Ca^{2+} -ATPase kinetics (V_{max} , Ca^{2+} affinity) and ER store dynamics for p.Pro602Leu versus representative Darier LOF alleles in keratinocytes/organoids to explain the milder phenotype.
2. **AVH-specific lesional sequencing:** Apply the paired lesional-vs-blood deep-sequencing strategy ([PMID: 38536168](#)) directly to persistent AVH papules to test whether second-hit somatic *ATP2A2* variants drive AVH lesion persistence as in Darier disease.
3. **Transcriptomic/desmosomal profiling of AVH skin:** Characterize desmosomal protein localization, barrier-gene expression (e.g., claudin-4, cadherin-4), and differentiation markers in AVH versus Darier versus normal acral epidermis.
4. **Natural-history / registry study:** Establish a multicenter AVH registry to estimate prevalence, define penetrance/expressivity, document nail involvement frequency, and formally assess any long-term malignancy risk.

5. **Comparative treatment evaluation:** Prospectively compare ablative modalities (cryotherapy, laser) ± retinoids/keratolytics for durable clearance and recurrence rates, given current reliance on anecdotal responses.
 6. **Humanized/organoid AVH model:** Engineer p.Pro602Leu into human epidermal organoids/iPSC-keratinocytes to create a dedicated AVH model distinct from Darier LOF models and test candidate SERCA2-modulating interventions.
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Report compiled from 11 confirmed findings across 19 reviewed papers (5 completed investigation iterations). Evidence types span human clinical case reports/series, model-organism (mouse), and in vitro/organoid studies, as annotated per section.

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