



Narrative review

Beyond the Surface: Porokeratotic Eccrine Nevus as a Marker of Genetic Mosaicism and Potential Malignancy

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ABSTRACT

Porokeratotic eccrine ostial and dermal duct nevus (PEODDN) is a rare skin condition that usually appears as clusters of thickened, wart-like bumps tracing the body's natural skin lines. While it's generally considered harmless, there's growing evidence that it may sometimes evolve into skin cancer, particularly squamous cell carcinoma. Recent research suggests that the condition may stem from mosaic mutations in the GJB2 gene specifically affecting a protein called connexin 26, which plays a key role in how skin cells and sweat glands communicate. This narrative review aims to be the first comprehensive synthesis that brings together what we currently know about PEODDN, from how it looks and behaves to the genetic factors behind it and the risk of it turning cancerous. A central focus is the role of connexin 26 dysfunction in breaking down the normal interactions between skin layers and sweat gland ducts. We also highlight a major gap in the research: there's still no clear model linking the underlying genetic changes to the skin changes we see under the microscope, how the condition progresses over time, or the likelihood of cancer. We conducted a comprehensive review of studies published from 2015 to 2025, using databases like PubMed, Scopus, and Web of Science. We focused on articles that explored the genetics, clinical features, risk of malignancy, or treatments for PEODDN. Only English-language studies with full-text access were included. Our aim was to identify patterns, highlight knowledge gaps, and suggest directions for future research. Across the literature, mosaic mutations in GJB2 and the resulting issues with connexin 26 emerge as a recurring theme in how this condition starts and possibly leads to cancer. Yet, despite numerous case studies, there's still no unified explanation that connects these genetic findings to the clinical course or cancer risk. There are no formal guidelines for monitoring patients, and current treatments mainly surgical removal or laser therapy offer mixed results. This review offers a new way of looking at PEODDN by tying together its clinical, genetic, and cancer-related aspects. We propose a working model that connects connexin dysfunction to both the development of lesions and the possibility of malignancy. There's a clear need for standardized diagnostic tools, long-term monitoring protocols, and genetic counseling for patients with widespread or unusual presentations.

1. Introduction

Porokeratotic Eccrine Ostial and Dermal Duct Nevus (PEODDN) is a rare cutaneous hamartomatous disorder distinguished by abnormal keratinization involving the eccrine sweat glands (particularly the acrosyringium) and by characteristic histologic features, including cornoid lamellae. Clinically, patients typically present with multiple punctate or keratotic papules that are often localized to the palms or soles. These lesions frequently follow linear or blaschkoid patterns, reflecting mosaic epidermal cell migration established during embryogenesis.

Epidemiologically, PEODDN remains exceedingly uncommon. Until recently, estimates often cited “fewer than 100 documented cases” in the literature. A review in 2021 reported at least 81 cases identified; more recent case reports and series continue to add new instances, including atypical adult-onset and solitary lesion presentations. There is no clear gender predilection, and though most cases are congenital or manifest in infancy or early childhood, there is a nontrivial proportion of late-onset cases. At the molecular level, recent advances have strengthened the hypothesis that PEODDN is a mosaic skin disorder caused by somatic mutations, particularly in GJB2 (the gene encoding connexin-26). Studies have identified somatic GJB2 mutations in

affected tissue that are absent in unaffected skin, supporting post-zygotic mutation and clonal expansion of altered epidermal cells. The mosaicism model aligns with the linear (Blaschkoid) distribution of lesions and with the observed variability in clinical presentation—even among patients with similar genetic findings.

In terms of clinical behavior, while PEODDN lesions are generally benign and asymptomatic, there have been reports of malignant transformation, most notably squamous cell carcinoma arising within long-standing lesions. Also, associations with other conditions—such as sensory polyneuropathy, hyperthyroidism, deafness, breast hypoplasia, and even systemic manifestations—have been documented, suggesting that even though the disease is primarily skin-limited, its impact can be broader in certain cases.

Given the rarity of PEODDN, the variability of its onset, presentation, and associated risks, there remains a need for comprehensive reviews integrating the most recent epidemiologic, genetic, and clinical data. This review aims to synthesize these findings in order to aid recognition, diagnosis, risk stratification, and management of PEODDN, and to highlight gaps for future research.

2. Clinical and Histologic Features of PEODDN

Typical lesion morphology of porokeratotic eccrine ostial and dermal duct nevus (PEODDN) comprises linear arrays of pinpoint to filiform, spiny keratotic papules that may coalesce into verrucous plaques; lesions can occasionally form cutaneous horn-like projections and often involve acral skin, including palms/soles, with ostial keratotic plugs visible clinically (1). Many cases are congenital or arise in early childhood (2). The disease may be widespread or remain localized and can be asymptomatic or pruritic (3). The cornoid lamella, a thin column of tightly packed parakeratotic cells overlying an area of epidermal dyskeratosis, is typically centered over eccrine ducts, which distinguishes PEODDN from other porokeratoses and epidermal nevi.

The distribution of PEODDN characteristically follows the lines of Blaschko in linear or whorled patterns, reflecting mosaicism (4). The involvement may be unilateral or, less commonly, extensive and bilateral and widespread (4). Blaschkoid distribution across extremities and trunk has been repeatedly documented,

with frequent distal extremity predominance and palmo-plantar extension (4). Rarely, atypical presentations have been documented, including localized, non-Blaschkoid or segmental lesions, and rare cases with systematized or widespread involvement (5). While the Blaschkoid distribution is most common, the diagnosis of PEODDN should not be excluded solely based on atypical or non-Blaschkoid presentation.

Histopathology typically reveals hallmark porokeratotic columns (cornoid lamellae) originating from adnexal ostia (6). This is most commonly found in the eccrine acrosyringia and, in some cases, hair follicles that are overlying areas of acanthosis and hyperkeratosis (6). Serial sections may demonstrate direct continuity with the eccrine ductal openings. Common misdiagnoses include inflammatory linear verrucous epidermal nevus (ILVEN), linear porokeratosis, linear epidermal nevus, viral warts, linear psoriasis, and other keratinization disorders. Key clinical features and differential diagnoses are summarized in Table I.

Table I. *Summary of clinical features and differential diagnosis.*

Category	Summary
Typical age at onset	Congenital or early childhood (rarely later)
Morphology	Linear arrays of small, spiny or filiform hyperkeratotic papules; may coalesce into verrucous plaques; ostial keratotic plugs often visible; occasional cutaneous horn-like projections
Distribution	Acral predilection (palms, soles, distal extremities); localized or widespread/systematized involvement; commonly follows lines of Blaschko in linear, whorled, or blaschkoid patterns; unilateral or extensive bilateral in systematized cases
Symptoms	Often asymptomatic; pruritus possible
Histopathology	Hyperkeratosis and acanthosis with hallmark porokeratotic columns (cornoid lamellae) arising from adnexal ostia—classically eccrine acrosyringia—with parakeratotic plugs and diminished/absent granular layer; serial sections may show continuity with eccrine ducts; occasional follicular involvement
Genetics	Somatic GJB2 mutations in mosaic pattern identified in subset of cases
Differential diagnosis	Inflammatory linear verrucous epidermal nevus (ILVEN); linear porokeratosis; linear epidermal nevus; verruca vulgaris; linear psoriasis; other keratinization disorders
Distinguishing clues	Adnexal-based cornoid lamellae favor PEODDN/PAON over classic porokeratosis variants
Associated findings	Rare extracutaneous anomalies; very rare malignant transformation in widespread disease—surveillance recommended in extensive cases
Treatment Options	Topical keratolytics, retinoids, cryotherapy, CO ₂ laser, surgical excision; variable efficacy

Out of these, ILVEN and linear porokeratosis are particularly challenging to differentiate from PEODDN since both can present with linear, verrucous, or psoriasiform lesions. Linear psoriasis can also mimic PEOD-

DN, especially if distributed along Blaschko's lines. Clinical annularity alone is insufficient for diagnosis; the presence of adnexal-based cornoid lamellae favors PEODDN over classic porokeratosis variants (6).

3. Genetic Mosaicism and the Role of *GJB2*

Postzygotic mosaicism provides a compelling explanation for the emergence of PEODDN, evidenced by molecular studies showing pathogenic GJB2 mutations present exclusively in lesional skin. For example, whole-exome sequencing revealed a somatic p.Gly45Glu (G45E) mutation in GJB2, observed in affected tissue but absent in blood, confirming that a somatic mutation alone suffices to produce PEODDN lesions (7). Another case identified both a germline heterozygous and a postzygotic somatic GJB2 mutation in PEODDN tissue, indicating that compound mosaicism may broad-

den the mutational spectrum and contribute to disease phenotype (8). Broader reviews affirm that PEODDN results from GJB2 (Cx26) mutations confined to affected keratinocytes, consistent with mosaic forms of keratitis-ichthyosis-deafness (KID) syndrome, and emphasize the necessity of genetic counseling because of potential germline or gonadal involvement (9, 6). These findings reinforce a clear model wherein connexin 26 disruption via postzygotic mosaicism underlies the localized skin pathology of PEODDN and carries reproductive implications.

Connexin 26 (GJB2) encodes a gap-junction protein essential for intercellular communication, forming connexons that permit ions and signaling molecules to pass between adjacent epidermal and eccrine duct cells (10). Mutations affecting the protein's structure can impair docking, gating, or calcium regulation, thereby disrupting keratinocyte differentiation and eccrine duct function. In syndromic disorders such as KID syndrome, dominant GJB2 mutations similarly compromise skin and hearing through altered connexin function, offering

a mechanistic parallel to PEODDN (11, 12). Moreover, mosaic manifestations of “lethal” GJB2 mutations in conditions like spiny hyperkeratosis illustrate how the timing and localization of somatic mutations shape phenotype dramatically (6, 13). These parallels underscore that localized connexin-26 dysfunction not only drives the keratotic adnexal lesions seen in PEODDN, but may also confer an elevated risk of malignant transformation through disruption of cell–cell signaling.

4. Malignancy Risk: Case Reports and Molecular Clues

PEODDN has been considered a rare, benign hamartoma of abnormal keratinization with unclear pathogenesis, with fewer than 100 reported cases to date. It shares some overlapping clinical features with porocarcinoma a malignant adnexal neoplasm with nuclear pleomorphism, atypical mitoses, and invasive growth patterns (14). However, the typical histologic presentation of PEODDN lacks these malignant cytologic features, distancing it from malignancy. Despite this, rare associations of PEODDN with squamous cell carcinoma (SCC) have been reported, along with other associated conditions such as hyperthyroidism, sensory polyneuropathy, and developmental delays (15). These

associations suggest that PEODDN may represent a disorder with broader systemic conditions rather than being confined to a simple cutaneous process. In addition to two cases of SCC in situ have been described in PEODDN, one involving a lesion on the left sole and another presenting with widespread PEODDN with diffuse ulcers, Fang et al. reported the first case of PEODDN that progressed to metastatic SCC with lymph node (16). Altogether, these three cases indicate that although PEODDN is generally benign, it may carry a low but recognizable risk of malignant transformation and metastasis in certain clinical scenarios (Table II).

Table II. *Malignancy Risk Factors Reported in Porokeratotic Eccrine Ostial and Dermal Duct Nevus (PEODDN).*

Risk Factor	Description
Widespread or systematized involvement	Extensive cutaneous involvement increases the likelihood of secondary mutational events and chronic irritation, and has been observed in cases progressing to squamous cell carcinoma (SCC).
Ulceration or chronic erosion	Ulcerative lesions show increased cellular turnover and inflammation, creating a microenvironment prone to dysplasia and malignant transformation.
Long-standing duration	Long-persistent lesions may accumulate additional somatic mutations over time, facilitating progression from benign hamartoma to SCC in situ or invasive SCC.
Compound or second-hit GJB2 mutations	The presence of both germline and somatic GJB2 mutations (or additional somatic oncogenic mutations) results in greater connexin-26 dysfunction and genomic instability.
Delayed or missed diagnosis	Misclassification as inflammatory or keratotic dermatosis may delay histologic confirmation and surveillance, allowing malignancy to remain unnoticed.
Coexisting chronic inflammation	Overlapping inflammatory conditions may promote keratinocyte atypia and accelerate oncogenic pathways.
Underrepresentation in skin-of-color diagnostic references	Reduced contrast and variability in lesion appearance may lead to diagnostic delay in patients with darker skin tones, prolonging exposure of affected cells to oncogenic triggers.

5. Management Strategies and Therapeutic Outcomes

There are no standardized treatment guidelines for PEODDN, and only limited therapies have been described in the literature. Reported management strategies range from conservative observation to procedural intervention, with treatment decisions typically guided by lesion extent, symptom burden, and concern for malignant transformation. Spontaneous resolution has been reported, and as lesions are often asymptomatic, PEODDN may not always warrant treatment (14, 20-22). In such cases, careful observation with periodic follow-up may be an appropriate strategy. When therapy is pursued, conventional topical treatments such as corticosteroids, keratolytic agents, and topical retinoids have generally shown limited efficacy (23, 24). One group reported the first successful use of topical flufenamic acid (FFA), a hemichannel inhibitor that improved skin lesions in mouse models carrying GJB2 gene variants (24). This targeted approach may hold promise for patients with confirmed connexin 26 mutations. Beyond topicals, systemic retinoids have shown mixed results, with favorable outcomes only in select cases (25). Overall, medical approaches have shown inconsistent results with no clear evidence to guide best practice.

Procedural interventions are another avenue of treatment for PEODDN. For localized disease, surgical

excision via shave removal, for instance, offers histopathologic confirmation and the potential for complete removal, making it particularly suitable for small, well-circumscribed lesions (26-28). Ablative laser techniques, most notably CO2 laser and combined erbium/CO2 laser, have shown great promise due to favorable short-term improvement and cosmetic outcomes (14, 28). However, recurrence rates remain poorly characterized due to limited long-term follow up. Significant gaps persist in PEODDN care, including the absence of evidence-based treatment algorithms, lack of long-term outcome data, and minimal patient-reported quality of life assessments. Recurrence rates following excision or laser therapy are unknown, and the durability of medical interventions is uncertain. The possibility of progression to squamous cell carcinoma (29) further complicates management decisions, emphasizing the need for shared decision-making with patients regarding treatment benefits and risks, structured surveillance protocols, and thresholds for prophylactic excision. There is currently no consensus on malignancy risk stratification or the role of genetic counseling. Addressing these unmet needs will require multicenter registries, randomized controlled trials, and prospective longitudinal follow-up.

6. Diagnostic Limitations and Differential Considerations

Porokeratotic eccrine ostial and dermal duct nevus (PEODDN) often presents diagnostic challenges due to its rarity, fewer than 100 reported cases, and variable clinical presentation. Due to its punctate or linear keratotic papules and Blaschkoid distribution, it is often mistaken for common dermatologic entities such as comedo nevus or linear porokeratosis. While PEODDN is traditionally considered a pediatric condition, in some cases, patients with solitary adult-onset lesions have been initially misdiagnosed as inflammatory or common keratotic dermatoses, delaying appropriate treatment. For example, one reported case involved a late-onset, solitary ankle lesion in a 64-year-old, emphasizing that PEODDN can present atypically (14). This puzzled clinicians who were accustomed to pediatric presentations. This case highlights the importance of including PEODDN in the differential diagnosis for solitary lesions in atypical locations, even in older patients. Bandyopadhyay et al. expanded upon this by presenting a detailed case of a 23-year-old man with

linear lesions on the palm and forearm, where PEODDN was initially mistaken for inflammatory dermatoses (30).

PEODDN recognition can be more challenging in patients with darker skin tones due to their underrepresentation in dermatologic literature and educational resources. Alvarado et al. (31) expand upon this by examining how dermatology educational materials, such as textbooks, online cases, and atlases, predominantly feature lighter skin tones. This imbalance impairs clinicians' ability to recognize dermatological conditions on darker skin tones. For example, one patient with a rash was diagnosed with toxic epidermal necrolysis but waited in the emergency room for several hours because the natural pigmentation of their skin made the "characteristic" redness that dermatologists look for appear far more subtle (32). Unfamiliarity with darker skin often contributes to the delay in diagnosis and treatment for this patient. This underrepresentation extends to artificial intelligence diagnostic models, which depict decre-

ased performance on images from patients with skin of color, especially for rare conditions such as PEODDN (33). The reduced contrast and pigmentation variations regularly mask important features, contributing to delayed or missed diagnoses. Integrating skin-of-color clinical presentations and image databases into dermatologic education will enhance representation and improve early recognition for PEODDN in all skin types.

Furthermore, another factor for diagnostic delays for PEODDN is the histologic overlap with other common dermatologic disorders. Under the microscope, PEODDN reveals a hallmark coronoid lamella overlying dilated acrosyringia, accompanied by loss of the granular layer and occasional dyskeratosis (34, 35). However, similar coronoid lamellae can be seen in linear porokeratosis or porokeratosis of Mibelli, potentially misleading interpretation (14). Nevus comedonicus can also mimic the clinical appearance, especially in locations lacking pilosebaceous units, such as palms and soles. In addition, inflammatory linear verrucous epidermal nevus (ILVEN), linear psoriasis, and other adnexal hamartomas often overlap histologically, further confu-

sing the diagnostic picture (35). Therefore, close collaborations between dermatologists and pathologists are often needed.

Finally, PEODDN is now understood to arise from somatic mosaic mutations in the GJB2 gene affecting connexin 26. Awareness of its genetic basis can help prompt consideration of PEODDN in atypical or ambiguous presentations (36). Understanding the role of GJB2 mutations not only accounts for the mosaic distribution pattern but also provides a framework for interpreting unusual cases. Chang et al. explained a “two-hit” model, in which a germline heterozygous GJB2 mutation is followed by a postzygotic somatic mutation, as shown in an 18-year-old female with congenital, linear hyperkeratotic papules on the fingers (37). This dual-mutation mechanism may explain the variability in lesion morphology and why clinicopathologic findings can at times be equivocal. Thus, improved clinical recognition combined with genetic insights will reduce misdiagnosis and delays in treatment.

7. Future Research and Surveillance Guidelines

Molecular and Genetic Investigations

Future investigations into PEODDN, a rare adnexal hamartoma, should prioritize elucidating its molecular underpinnings, particularly its association with postzygotic mosaic mutations in GJB2, which encodes connexin-26. These mutations have been identified in both isolated lesions and syndromic presentations, supporting a broader spectrum of connexin-related mosaic disorders (38-40). Further research should aim to uncover additional genetic drivers through whole-exome or targeted sequencing of lesional tissue, focusing on disrupted eccrine gland development and keratinization pathways (41, 42). In vivo systems and patient-derived

organoids may help clarify the downstream effects of these mutations and their potential to trigger secondary neoplastic transformation. Spatial transcriptomics also offers a promising tool to map aberrant signaling pathways and cellular interactions within lesional microenvironments, which may uncover novel molecular targets (43, 44). Incorporating molecular profiling into diagnostic workflows may improve subtype classification, inform prognosis, and guide genetic counseling, especially for patients with congenital or widespread disease.

Surveillance and Clinical Management Protocols

Surveillance strategies should evolve in tandem with these molecular insights, especially given PEODDN's variable clinical course and potential for malignant transformation. Although traditionally regarded as benign, several case reports have documented squamous cell carcinoma arising within longstanding lesions (45-47). Evidence-based monitoring protocols should combine dermatologic imaging techniques—such as dermoscopy or reflectance confocal microscopy—with

symptom tracking and periodic biopsy to guide intervention thresholds. Because many lesions follow a Blaschkoid distribution, suggestive of early embryonic mosaicism, systemic evaluation is warranted in congenital or extensive presentations to identify possible extracutaneous involvement (9, 11). Quality-of-life assessments should be incorporated into routine care, as PEODDN may cause pruritus, pain, or psychosocial distress depending on location and extent. AI-assisted

image analysis and digital lesion tracking may further enhance surveillance accuracy and reduce interobserver variability. Ultimately, interdisciplinary collaboration across dermatology, genetics, oncology, and pathology

will be essential to develop comprehensive surveillance algorithms that reflect both clinical variability and emerging molecular insights.

7. Discussion

Molecular

The extremely uncommon adnexal hamartoma known as Porokeratotic Eccrine Ostial and Dermal Duct Nevus (PEODDN) is characterized by aberrant keratinization surrounding eccrine acrosyringia. It frequently manifests as linear or whorled patterns that follow the lines of Blaschko. PEODDN, which was formerly thought to be a benign congenital or early-onset disease, is now understood to be a postzygotic mosaic condition, mostly caused by somatic mutations in GJB2. The idea of embryonic mosaicism is supported by the finding of

connexin-26 mutations limited to lesional tissue, which explains both the localized distribution and the broad range of clinical phenotypes, from solitary filiform papules to systematized dermal involvement across multiple body segments. These molecular insights have also shifted the clinical understanding of PEODDN, suggesting potential reproductive implications, particularly in patients harboring compound germline and somatic mutations.

Clinical Evidence

The majority of PEODDN lesions are stable and asymptomatic, and conservative treatment is frequently used. For isolated, asymptomatic lesions, observation with recurring follow-up is suitable. Although long-term recurrence rates are unclear, ablative CO₂ laser therapy and surgical excision have shown promising results for lesions that are symptomatic or cosmetically

problematic. The potential for molecularly guided interventions is shown by newly developed targeted medications such as topical flufenamic acid, which inhibits connexin hemichannels. Developmental delay, hyperthyroidism, and sensory polyneuropathy are examples of extracutaneous symptoms that suggest the clinical spectrum may be wider than previously thought.

8. Case-Based Reports and Oncogenic Potential

Squamous cell carcinoma in situ and even metastatic squamous cell carcinoma originating inside long-standing or widespread PEODDN lesions have been reported in case reports, however they are uncommon. PEODDN may act as a precursor in a multi-step tumo-

rogenesis pathway involving dysregulated gap-junction signaling and impaired keratinocyte differentiation. Malignant progression seems more likely in the context of chronic ulceration, widespread distribution, or presumed second-hit genetic events.

9. Recommendations and Future Directions

Advanced diagnostic techniques including dermoscopy, reflectance confocal microscopy, and digital lesion tracking should be used in surveillance regimens to maximize patient care and reduce the risk of cancer. For developing or ulcerated lesions, especially those with systematized or congenital distribution patterns, a low threshold for biopsy is advised. Reducing recognition disparities requires more skin-of-color photos to be included in training materials and diagnostic datasets.

To create evidence-based risk stratification tools, improve diagnostic frameworks, and direct targeted therapies, long-term, multi-institutional cooperation and longitudinal data gathering will be essential. Precise diagnosis and better long-term results for individuals with PEODDN will require a multidisciplinary approach encompassing dermatology, pathology, clinical genetics, and oncology.

Authors Declare No Conflict of Interest

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