Coexistence of acne inversa with psoriasis and Dowling-Degos disease harboring impaired PSENEN-Notch signaling

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To the Editor: Acne inversa (AI), also known as hidradenitis suppurativa, is a chronic recurrent inflammatory skin disease characterized by deep painful nodules and abscesses with resultant scarring mainly distributed in intertriginous areas. Loss-of-function mutations in γ-secretase (GS) genes are responsible for familial AI.[1] GS is a transmembrane protease composed of four essential protein subunits: one catalytic presenilin subunit (PSEN) and three cofactor subunits (nicastrin [NCSTN], presenilin enhancer 2 [PSENEN], anterior pharynx defective 1). GS is involved in cleavage of various type I membrane proteins, including amyloid precursor protein and Notch proteins. PSENEN directly binds to PSEN and is required for its autocatalytic cleavage and protease activity. To date, six mutations have been reported in *PSENEN*, all of which result in frameshift truncations and altered protein products, predominantly leading to haploinsufficiency.[2] Psoriasis is a genetically-determined proliferative and inflammatory entity, resulting from complex interactions between aberrant keratinocyte proliferation and differentiation, and a T-lymphocyte-mediated immune process. Dowling-Degos disease (DDD), a rare autosomal dominant disorder, is characterized by progressive reticulate hyperpigmentation and small dark-brown hyperkeratotic papules, mainly affecting flexural areas.[3] Herein, we report a proband and three other members of a three-generation Chinese Han AI family with co-occurrence of psoriasis and DDD, respectively.

The 20-year-old male proband [III:5 in Figure 1A] presented with a 4-year relapsing history of multiple separated comedones, inflammatory papules, pustules, painful nodules, and cysts particularly located on the nape, upper back, and buttocks [Figure 1B and 1C]. At 1 year after the initial manifestations, he was afflicted by a concomitant itchy eruption characterized by scattered erythematous papules and macules with silvery-white lamellar scales mainly on the scalp and extremities, distinguishing itself from earlier lesions [Figure 1D]. Histopathological examination of an inflammatory nodule from the buttocks and a scaly papule from the forearm showed destruction of pilosebaceous follicles with surrounding marked fibrosis [Figure 1E] and regular acanthosis, confluent parakeratosis, and hypogranulosis with formation of a Munro microabscess [Figure 1F], respectively. Based on these findings, we diagnosed the patient with concomitant AI (Hurley stage I) and psoriasis. His 48-year-old mother (II:5) had similar, but more severe, inflammatory AI lesions with hypertrophic scars involving the nape, upper trunk, axillae, groins, and buttocks since puberty (Hurley stage II) [Figure 1 G–K]. Intriguingly, she also showed extensive comedones, pitted scars, and macular or reticulate hyperpigmentation located at flexural areas and the face, reminiscent of DDD [Figure 1 G–L]. The other six family members manifested either AI lesions (II:3, II:7, III:2, III:3) or AI-DDD lesions (I:2, II:1) with varying severity, revealing an autosomal dominant inheritance pattern [Figure 1A].

The study was approved by the Institutional Ethical Review Boards of the Union Hospital of Fujian Medical University (No. 2019WSJK023). After receiving informed consent, we analyzed the entire coding regions and proximal flanking intronic sequences of the GS genes in the family by Sanger sequencing. In the proband and his mother, a heterozygous frameshift c.66delG mutation in exon 3 of the *PSENEN* gene was detected. This mutation segregated with affected, but not unaffected, family members, and was not observed in 100 control individuals [Figure 1M]. Remarkably, it was a recurrent mutation resulting in a premature termination codon (p.F23LfsX46).[2] Next, we extracted mRNA from peripheral lymphocytes of five AI patients in the family (I:2, II:1, II:3, II:5, III:5) and five normal non-consanguineous controls, and detected the relative PSENEN-Notch signaling molecule mRNA levels by real-time quantitative polymerase chain reaction. Compared with the controls, the patients

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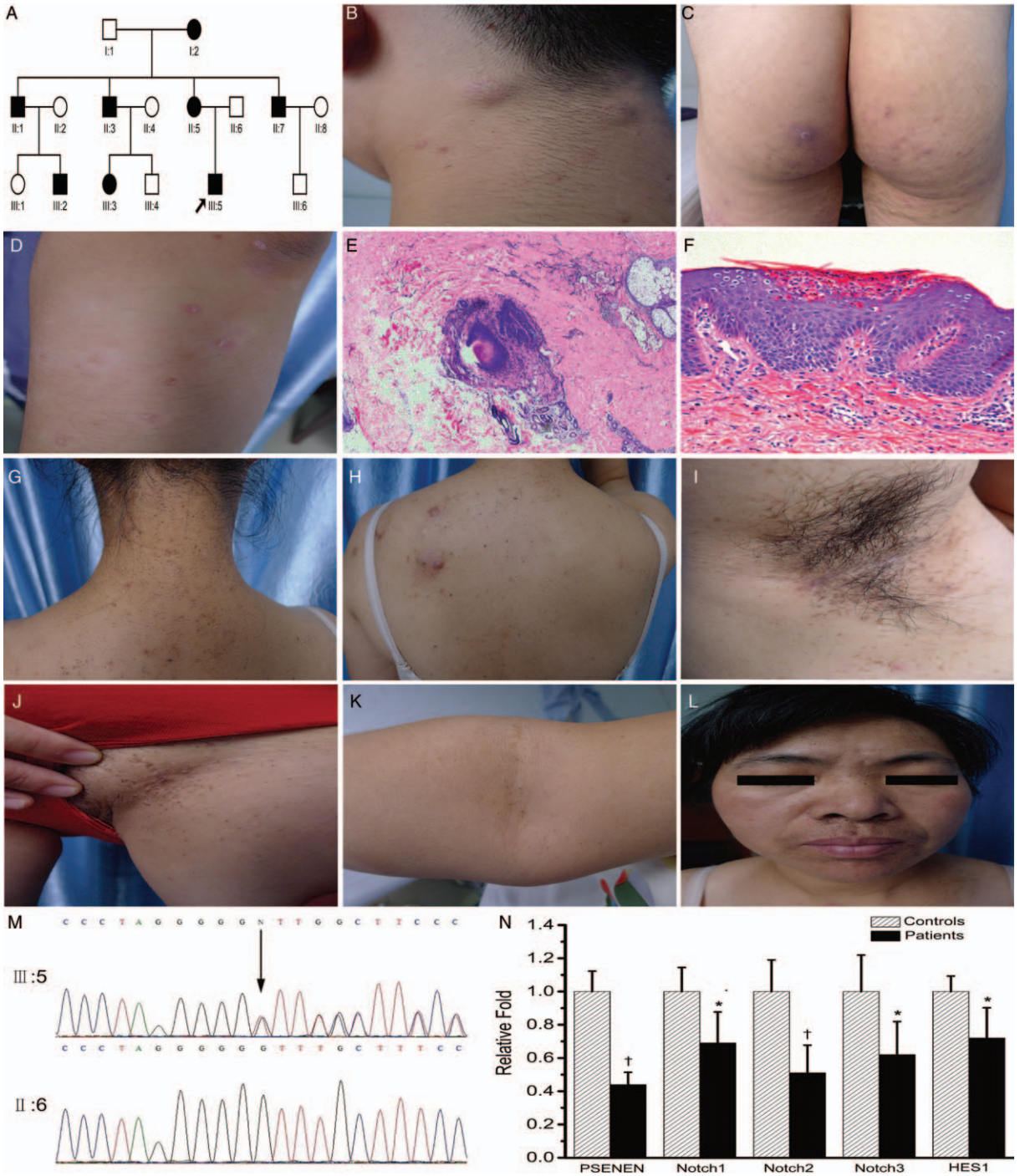

Figure 1: Pedigree tree of the family (A). Clinical and histopathological findings in the proband of the pedigree (B–F): papules, pustules, nodules and cysts on the nape (B) and buttocks (C); erythematous papules and macules with slivery white lamellar scales on the extremities (D); histopathology of biopsies taken from the nape:destruction of pilosebaceous follicles with surrounding marked fibrosis (E, Hematoxylin-eosin staining, original magnification ×50); histopathology of biopsies taken from the forearm: regular acanthosis, confluent parakeratosis, hypogranulosis, and the formation of "Munro microabscess" (F, Hematoxylin-eosin staining, original magnification ×200). Clinical features of the proband's mother (G–L). Papules, pustules, nodules, cysts and hypertrophic scars on the nape (G), upper trunk (H), axillae (I), groins (J), and buttocks (K); besides, extensive comedones, pitted scars, and macular or reticulate hyperpigmentation are shown in flexural areas (I–K) and face (L). A heterozygous frameshift mutation c.66delG (p.F23LfsX46) was identified in the proband while was absent in unaffected II:6 (M). Comparison of the transcription levels of PSENEN-Notch signaling between the patients and healthy controls ($n = 5$) (N, $^{*}P < 0.05$ and $^{\dagger}P < 0.01$).

exhibited remarkable reductions in PSENEN mRNA expression, indicating that the mutant was subjected to nonsense-mediated decay and resulted in loss-of-function. Meanwhile, Notch molecules including Notch1–3 and target gene *HES1* were significantly suppressed in the patients, signifying that *PSENEN* haploinsufficiency contributed to deficiency in Notch signaling activity [Figure 1N].

The coexistence of AI and psoriasis in our case was probably not coincidental, because a recent study revealed that 28 of 440 AI patients manifested concomitant

psoriasis vulgaris (6.4%).[4] Interestingly, similar to our case, hyperkeratosis and psoriasiform hyperplasia of the interfollicular epidermis with subepidermal inflammatory infiltrates are often observed in AI, resembling those evident in psoriasis. PSENEN is involved in intracellular cleavage of Notch proteins, which is necessary for activation of Notch signaling. Inherited or acquired impairment of Notch signaling is hypothesized to be the primary pathogenic event in AI. Within the epidermis, Notch signaling is involved in epidermal cell differentiation, hair follicular terminal differentiation, and epidermal proliferation.[1] Consistent with its role in hindering proliferation and promoting differentiation of keratinocytes, expression of Notch signaling is also decreased in psoriasis, characterized by hyperproliferation and disturbed differentiation of keratinocytes. Moreover, tumor necrosis factor-α and interleukin-12/23 inhibitors have demonstrated utility in AI, suggesting that the inflammation cascade is implicated in its pathogenesis, similar to psoriasis. Notch signaling is also a significant regulator of T-lymphocyte-mediated immune responses because it serves as a feedback repressor of over-activated natural immunity. Impaired Notch signaling may cause excessive proinflammatory macrophage cytokine expression (tumor necrosis factor-α, interleukin-1β, interleukin-23), thereby triggering Th17-mediated immune responses.

Several cases of co-manifestation of AI-DDD with *PSENEN* mutations have been described, suggesting the possible existence of a common pathogenetic mechanism. Indeed, the two entities share important clinical and histopathological features including onset during puberty, flexural location, and follicular involvement. Only heterozygous mutations in *PSENEN* gave rise to pigmentation abnormalities including DDD, while the other two identified AI genes, *PSEN1* and *NCSTN*, were not mentioned.[3] The Notch pathway has an integral role in skin homeostasis by mediating melanocyte proliferation and differentiation, and orchestrating interactions between melanocytes and keratinocytes.[3] It is intriguing that *PSENEN* knockdown in zebrafish led to development of aberrant pigmentation, resembling the DDD phenotype. Similar compromised PSENEN-Notch signaling was observed in keratinocytes from patients with AI-DDD and isolated AI in a recent study.[5] Taken together, the findings imply that *PSENEN* mutations in AI may predispose patients to occurrence and development of DDD through disrupted Notch signaling.

The present report demonstrates three different phenotypes in one AI family: AI, AI-DDD, and AI-psoriasis. It is further suggested that diminished expression of PSENEN-Notch molecules may induce dysfunction of Notch signaling and be the unifying molecular mechanism underlying the significant phenotypic heterogeneity in this AI family.

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Conflicts of interest

None.

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