Psoriasis: Targets and Therapy

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CASE SERIES

# Acrodermatitis Continua of Hallopeau and Generalised Pustular Psoriasis: Case Reports of Two Different Manifestations of IL36RN Mutation in Siblings

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**Abstract:** In our manuscript, we present a case study of siblings with Generalized Pustular Psoriasis (GPP) and Acrodermatitis Continua of Hallopeau (ACH), both harboring IL36RN gene mutations. The 3-year-old proband exhibited systemic pustules leading to a GPP diagnosis, while his 6-year-old sister developed nail ulcers and subungual pustules characteristic of ACH. Despite standard treatments, their conditions were refractory. Genetic analysis revealed a homozygous splice variant c.115+6 T>C, with heterozygous parents. This case underscores the role of IL36RN mutations in pustular psoriasis and supports ACH as a localized form of the disease. The distinct subtypes in siblings with identical mutations suggest a complex pathogenesis influenced by additional factors. Our findings highlight the importance of genetic testing in pustular psoriasis and warrant further investigation into the phenotypic variability of IL36RN-related disease.

**Keywords:** Acrodermatitis Continua of Hallopeau, generalised pustular psoriasis, IL36RN gene mutations

Generalized Pustular Psoriasis (GPP) and Acrodermatitis Continua of Hallopeau (ACH) are both subtypes of Pustular Psoriasis, with ACH being classified by the Japanese Dermatological Association (JDA) as a subtype of GPP. We report a case of siblings, one diagnosed with GPP and the other with ACH, both identified with IL36RN-related gene mutations.

The proband, a 3-year-old boy, developed erythema and pustules on his abdomen and hands at 60 days old, which then spread systemically, leading to a GPP diagnosis. Despite treatment with methylprednisolone and acitretin, his condition persisted. Currently, the patient exhibits diffuse erythematous plaques with scattered pustules and fine white or honey-colored scales (Figure 1).

The second patient, his 6-year-old sister, was diagnosed with ACH at age 4 when she developed nail ulcers and subungual pustules on her fingers and toes. Treatment with cyclosporine, erythromycin, and halometasone was ineffective. Presently, she has nail ulcers and subungual abscesses on all five fingers of her right hand, the thumb, index, and little fingers of her left hand, and the fourth toe of her right foot, with accompanying periungual erythema and swelling (Figure 2).

Both patients exhibited symptoms early and belonged to the same family, prompting IL36RN gene Sanger sequencing. Genetic mutation analysis revealed a homozygous splice variant c.115+6 T>C in both patients, while their parents were heterozygous carriers (Figures 3 and 4).

Received: 18 October 2024
Accepted: 15 March 2025
Published: 26 March 2025

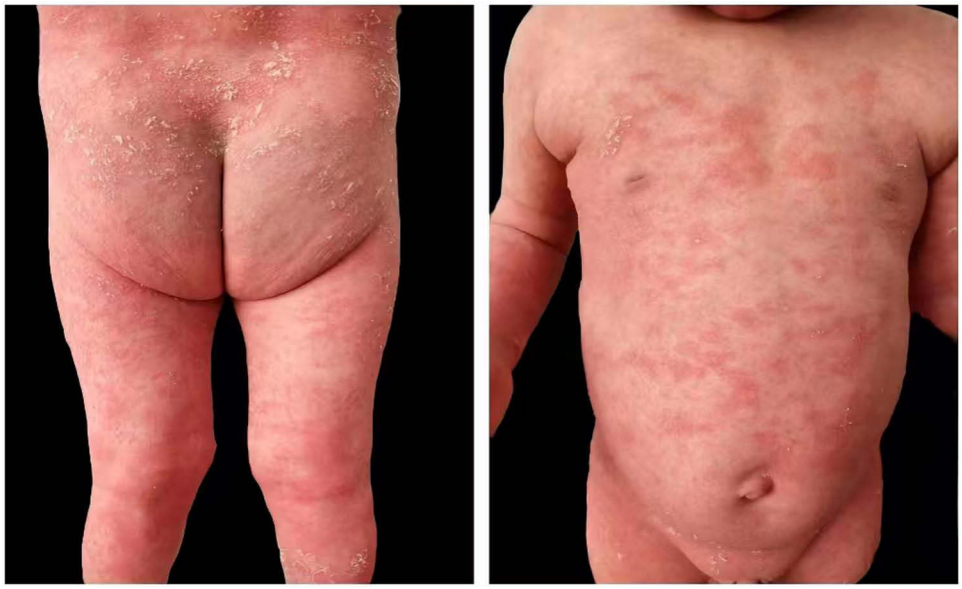

**Figure 1** The patient has widespread erythema, accompanied by scattered pustules and scales.

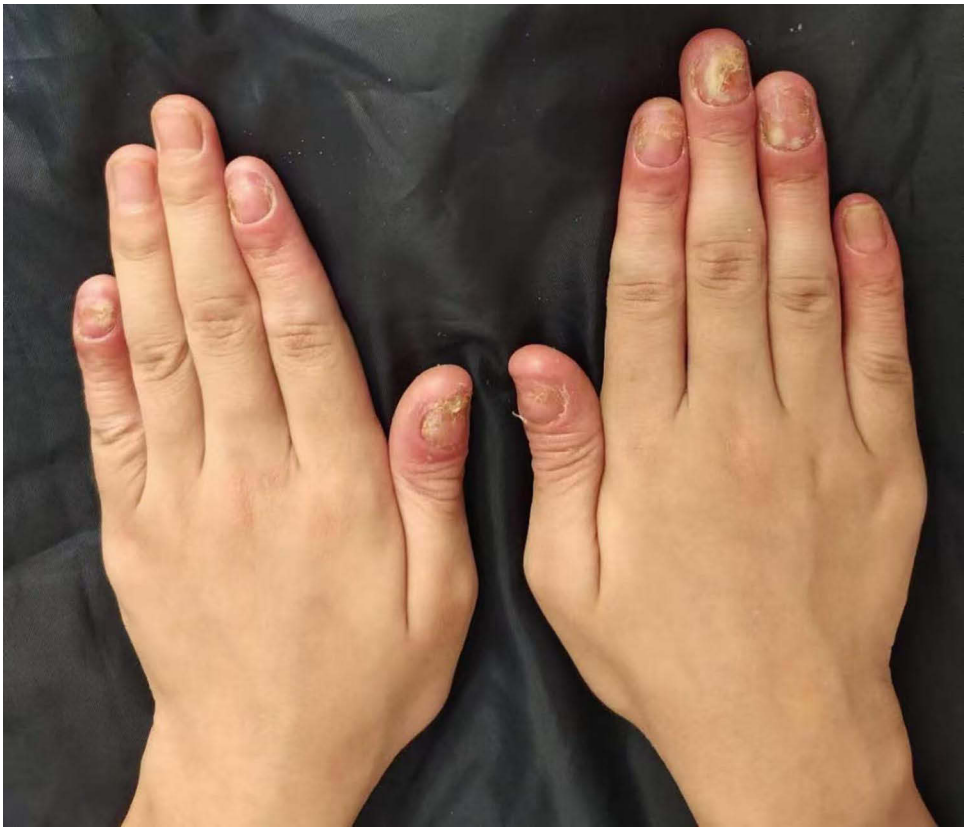

**Figure 2** The patient presents with nail ulcers and subungual abscesses on all five fingers of the right hand, the thumb, index finger, and little finger of the left hand, and the fourth toe of the right foot, accompanied by periungual erythema and swelling.

IL36RN encodes the IL-36 receptor antagonist (IL-36Ra), primarily expressed in the skin. Research shows IL-36 is overexpressed in GPP lesions, maintaining a neutrophil recruitment and activation loop critical in GPP pathogenesis. Unopposed IL-36 signaling due to loss-of-function mutations in IL36RN may lead to activation of the IL-36 signaling pathway and its main downstream NF-κB pathway.[1] Previous studies have identified IL36RN gene mutations as the basis of familial

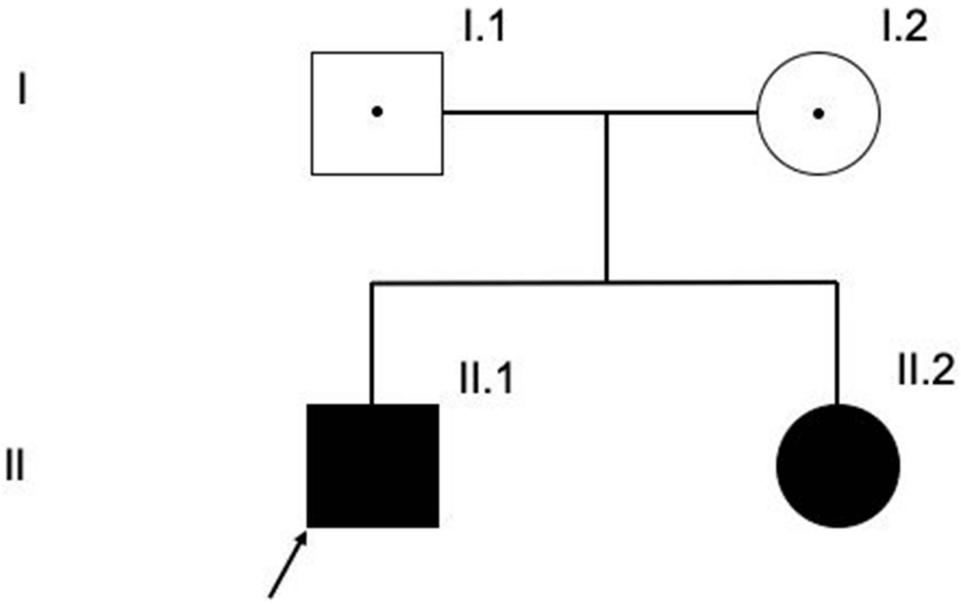


**Figure 3** Pedigree of family with black arrow pointing to the proband.

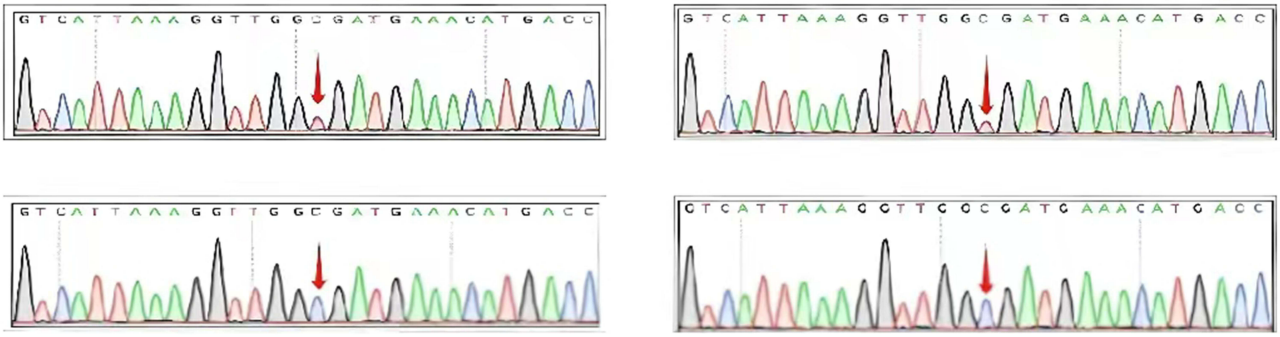

**Figure 4** Sanger sequencing confirmed a homozygous variation in IL36RN: c.115+6 T>C in the proband and his sister; the same variation was heterozygous in the parents. (red narrow).

GPP.[2] Similarly, Ossama Abbas et al reported siblings with ACH and GPP carrying homozygous mutations at the same IL36RN locus.[3] Sophie Twelves et al found IL-36RN mutation rates of 23.7% in GPP and 18.2% in ACH, highlighting these mutations as the most common genetic defects in these subtypes.[4] Analysis of GPP patients across multiple Asian countries revealed c.115+6 T>C as the most frequent mutation, suggesting a founder effect in the Asian population.[5–7] Wang et al further analyzed pustular psoriasis subtypes and c.115+6T>C mutations, showing that homozygous c.115+6T>C variants are highly enriched in pustular psoriasis, with the highest rate (93.8%) in GPP patients with ACH features.[8] Early onset is also a known risk factor for positive IL36RN mutations.

These two patients indicate that both GPP and ACH can result from IL36RN gene mutations, further proving that ACH represents a localized form of pustular psoriasis. The two pediatric cases with identical genetic mutations presented different pustular psoriasis subtypes, while the heterozygous parents remain unaffected, though future development of pustular psoriasis cannot be ruled out. Further studies are needed to comprehensively validate and elucidate the similarities and differences in the pathogenic mechanisms of IL36RN gene variants across pustular psoriasis subtypes.

## Data Sharing Statement

The datasets analyzed for this study are available from the corresponding author Dr. Chen Li (casio1981@163.com) upon reasonable request.


https://doi.org/10.2147/PTT.S498720

## Ethics Approval and Consent to Participate

This article was performed in accordance with the principles of Declaration of Helsinki. Ethical review and approval was not required to publish the case details in accordance with the local legislation and institutional requirements. Both patients' case details in the written informed consent was obtained from the patients' mother for publication of this case report and any accompanying images as per our standard institutional rules.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This work was supported by grants from the National Natural Science Foundation of China (grant number: 82074246; 82374272), the High-Level Chinese Medical Hospital Promotion Project (grant number: HLCMHPP2023027; HLCMHPP2023088), the Escort Project of Guang'anmen Hospital, China Academy of Chinese Medicine Science-Backbone Talent Cultivation Project (grant number: GAMHH9324021) and the Scientific Research Foundation for New recruits, China Academy of Chinese Medical Sciences (grant number: ZZ16-XRZ-045).

## Disclosure

The authors declare no competing interests in this work.

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