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CASE REPORT

E114G de Novo Mutation in GJB2 Gene in a Chinese Patient with Classical Vohwinkel Syndrome

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Abstract: Vohwinkel syndrome (VS) is a rare autosomal dominant form of palmoplantar keratoderma (PPK), characterized by diffuse hyperkeratosis of the palms and soles, starfish-shaped keratotic lesions, and pseudo-ainhum. Mutations in GJB2 have been implicated in VS pathogenesis. In this study, Sanger sequencing of the GJB2 coding exons and exon-intron boundaries was performed in a Chinese patient with VS. A missense mutation c.341A>G (E114G) was also identified. This finding expands the mutational spectrum of VS and provides further insight into its genetic basis, which may facilitate improved genetic screening and counseling of affected families.

Keywords: Vohwinkel syndrome, GJB2 mutation

Introduction

Vohwinkel syndrome (VS; OMIM #124500) is a rare autosomal dominant palmoplantar keratoderma (PPK), characterized by honeycomb-patterned hyperkeratosis, pseudo-ainhum, starfish-shaped acral keratosis, and frequent sensorineural deafness. VS is genetically heterogeneous, with causative mutations in both GJB2 and LOR.[1,2] GJB2 is located on chromosome 13q12, which encodes a component of intercellular gap junctions, connexin 26 (Cx26). In the epidermis, Cx26 is crucial for maintaining keratinocyte homeostasis. It facilitates intercellular communication that regulates keratinocyte proliferation, differentiation, and coordinated epidermal barrier function. Mutations in GJB2 can disrupt these critical processes, leading to the hyperkeratotic skin manifestations seen in VS and other syndromic deafness disorders such as Keratitis-Ichthyosis-Deafness (KID) syndrome. VS caused by a GJB2 mutation usually involves hearing loss and is associated with classical VS.

Here, we report a de novo mutation in a Chinese patient with VS and sensorineural deafness. To the best of our knowledge, this is the first reported case of E114G mutation worldwide. This finding expands the mutational spectrum of VS.

Mutation Detection

Genomic DNA was isolated from peripheral blood lymphocytes using the Qiagen FlexiGene DNA Kit (51206). The GJB2 reference sequences were obtained from the NCBI database. Primer pairs flanking all exons and exon-intron boundaries of GJB2 were designed using the Primer3 software. The PCR primers used were as follows: Forward: 5-ATGCTTGC TTACCCAGACTCA-3, Reverse: 5-GAGGCTTTAGGGGAGCAGAG-3. Each 20-μL reaction contained 1 × master mix, 0.2 μM of each primer, 20 ng genomic DNA, Nuclease-free water to volume. The thermocycling conditions were as follows: initial denaturation at 95°C for 10 minutes. 35 cycles of denaturation at 95°C for 10s, and annealing/extension at 60°C for 30s. The PCR products were purified and sequenced bidirectionally on an ABI 3730 XL Genetic Analyzer using the BigDye Terminator v3.1 Cycle Sequencing Kit. Electropherograms were analyzed using Sequencing Analysis Software and aligned to the reference sequence.

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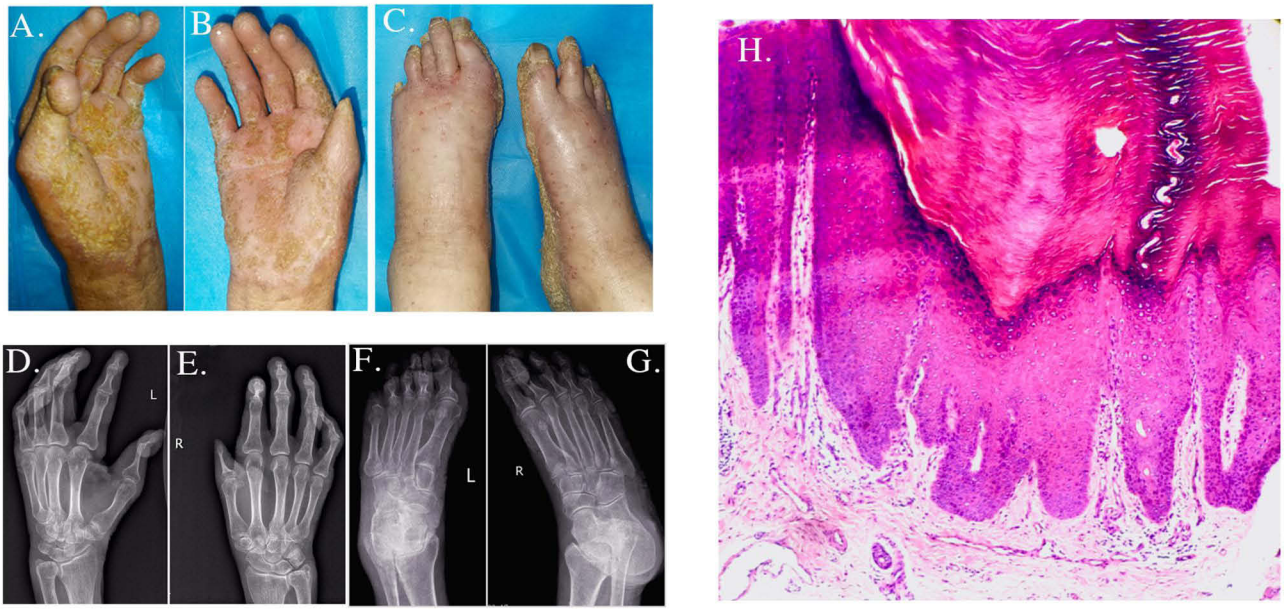

Figure 1 Clinical features of the patient. Diffuse palmoplantar hyperkeratosis was symmetrically distributed on both palms, fingers (**A** and **B**) and feet (**C**). Annular constriction and contractures were seen on the thumb and index finger of both hands (**A** and **B**). Autoamputation at the base of the left fifth toe (**C**). The X-ray examination showed bone density of hands and feet was decreasing and the 5th phalange of left foot was partially absent (**D**–**G**). Histological examination of a plantar hyperkeratotic lesion sample revealed hyperkeratosis, acanthosis and hypergranulosis (**H**) (HE; bar, 100 μm).

Results

Clinical Features

A 76-year-old Chinese woman presented to our hospital with bilateral diffuse palmoplantar hyperkeratosis without pseudo-ainhum (digit constriction bands). No other family member, including her daughter, husband, or grandson, exhibited similar symptoms.

Dermatological examination revealed symmetrical, diffuse hyperkeratosis affecting the palms, fingers, and soles. Annular constrictions with contractures of the thumb and index fingers were observed bilaterally (Figure 1A and B). Autoamputation was performed at the base of the left fifth toe (Figure 1C). The patient had no symptoms of ichthyosis. Radiological X-ray imaging revealed decreased bone density in the hands and feet, with partial absence of the fifth phalanx in the left foot (Figure 1D–G). Histological examination of the plantar hyperkeratotic lesions revealed hyperkeratosis, acanthosis, and hypergranulosis (Figure 1H). Audiometric testing showed bilateral sensorineural hearing loss (Supplementary Figure 1).

E114G Mutation in GJB2

Sanger sequencing of GJB2 using the patient's genomic DNA revealed a missense mutation c.341A>G (E114G) in the exon of GJB2 (Figure 2A and B). This mutation has not been reported previously. This substitution was not found in unaffected family members or in healthy controls, excluding polymorphisms in the GJB2 gene.

Discussion

VS, also known as keratoderma hereditary mutilans, is a rare complex genetic disorder. The incidence and prevalence of VS are extremely rare, with fewer than 50 cases reported in the literature. Males and females are equally affected by both children and adults. VS is associated with sensorineural hearing loss due to pathogenic mutations in GJB2. GJB2 encodes connexin 26, a component of the beta-2 gap junction protein composed of 226 amino acids.[3] Connexin proteins are transmembrane proteins that assemble into gap junctions and intercellular channels, which are critical for the exchange of ions, metabolites, and signaling molecules. These junctions facilitate coordinated cellular activities including potassium recycling in the inner ear, epidermal homeostasis, and neurotransmitter regulation. Gap junctions formed by connexin 26

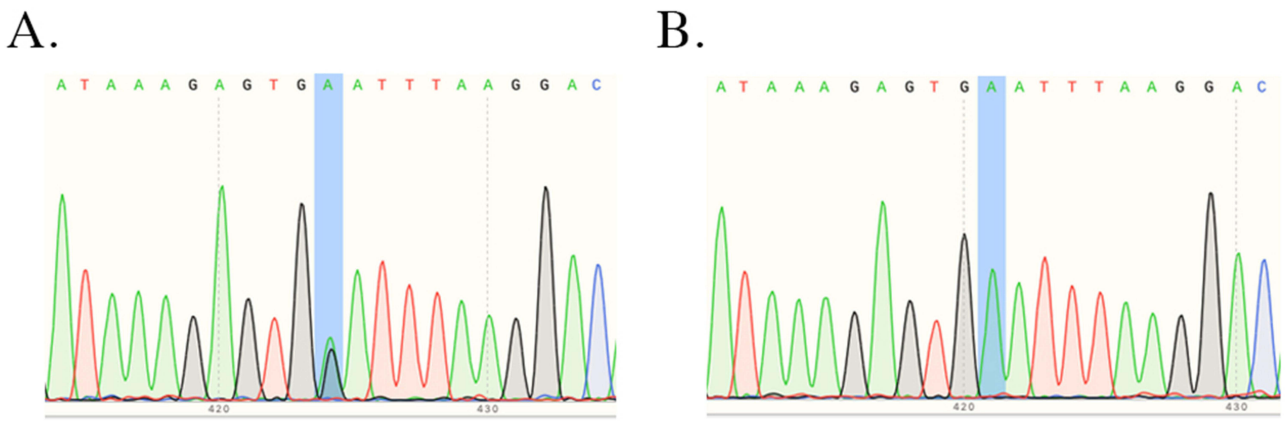

Figure 2 Identification of missense mutation in the exon of GJB2 gene. Missense mutation c.341A>G (E114G) in the patient (**A**) and control (**B**). The position of the mutation is indicated by blue background.

are essential for auditory function and facilitate potassium ion recycling within the cochlea.[4] This process converts mechanical sound waves into electrical nerve impulses, which are critical for normal hearing.[5] Thus, Cx26 connexin mutations are commonly associated with deafness.

Recently, emerging evidence suggests that mutated GJB2 dysregulates epidermal keratinocyte differentiation and proliferation, contributing to hyperkeratosis in VS. For instance, Djalilian et al demonstrated that Cx26 is critical for maintaining epidermal barrier integrity and orchestrating wound healing by modulating keratinocyte proliferation dynamics.[6] These findings imply that GJB2 mutations may disrupt intercellular communication, leading to aberrant keratinocyte activation and impaired terminal differentiation, a mechanism that aligns with hyperkeratotic and constrictive lesions characteristic of VS.

Syndromic palmoplantar keratodermas with deafness related to the dominant mutation in GJB2 include VS, keratitis-ichthyosis-deafness syndrome (KID) and Bart-Pumphrey syndromes (BPS). KID is characterized by keratitis and ichthyosis. BPS is distinguished by the presence of leukonychia and absence of constriction bands.[7,8] We diagnosed our case as classical VS based on the GJB2 mutation, presence of palmoplantar keratodermas, constriction bands, and absence of keratitis and ichthyosis. The late onset of symptoms in our patient (around age 72) is unusual for classical VS, which typically presents in infancy or childhood. This may be attributed to the specific functional impact of the E114G mutation, which could result in a milder or progressively deteriorating gap junction function over time.

Several heterozygous missense mutations, such as G59S, G59R, Y65H, D66H, H73R, and G130V, the GJB2 gene.[9–13] Interestingly, the disease course in our case was only > 4 years, which was different from that reported in early childhood, and the patient had no classical symptoms of starfish-like keratoses on the elbows or dorsa of the hands. Based on the mutational spectrum of VS, an exact one-to-one correspondence between specific GJB2 mutations and clinical symptoms does not exist because patients with the same mutation may display highly different phenotypes.[14] To date, while multiple heterozygous missense mutations have been associated with VS, this is the first reported case of the E114G mutation worldwide. We believe that this study expands the genotype-phenotype spectrum of VS. However, the exact etiology of VS remains unknown, and progressive research is still needed.

However, the use of VS treatment remains limited. Symptomatic treatments for VS aim to improve keratoderma and release the digital constriction bands. Surgery such as Z-plasty is commonly used to treat constriction bands (such as Z-plasty strategy).[15] Hyperkeratotic lesions are often improved with topical and oral retinoids such as isotretinoin.[16] Accumulating evidences support the use of low-dose oral retinoids to prevent the pseudo-ainhum.[17,18] Systemic retinoids can reverse both keratoderma and pseudo-ainhum. Recently, Ling et al reported that low doses of transforming growth factor β1 (TGF-β1) could improve VS proliferation by promoting keratinocyte proliferation.[19] In our case, following treatment with topical tretinoin ointment, the skin lesions improved within one month. However, the patient died two months after the examination.

This study has several limitations. Firstly, Firstly, we were unable to perform genetic testing on the patient's parents to confirm the de novo origin of the E114G mutation. Secondly, the patient's death two months after presentation remains an unexplained and unfortunate event, limiting our ability to assess long-term treatment outcomes.

In summary, we reported a Chinese case of Vohwinkel syndrome caused by de novo E114G mutation in the GJB2 gene. This finding expands the mutational spectrum of VS and underscores the importance of genetic screening in patients with atypical or late-onset presentation.

Ethics Statement

The study was approved by the Ethics Committee of Lujiang County People's Hospital, China (LYKYLL2025-0901). The patient's husband signed the written informed consent to participate in this project and consented the publishment of clinical details and relevant images. The institutional approval was not required for the publication of case details. The authors reported no conflict of interest.

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Disclosure

The authors report no conflicts of interest in this work.

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