An Unusual Missense Mutation in the *GJB3* Gene Resulting in Severe Erythrokeratodermia Variabilis

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Erythrokeratodermia variabilis (EKV, MIM ID #133200) is a rare congenital disorder, usually inherited as an autosomal dominant trait (1). EKV is clinically characterized by two morphological features; namely, more-or-less fixed hyperkeratoses and variable and transient red patches, both having geographical shape and distribution. Hyperkeratoses may be localized all over the body, in particular on the extensor surface of the extremities, buttocks, and lateral trunk, and often on the palms and soles. Erythematous patches vary in size, shape, and localization. A variety of mutations in the *GJB3* and *GJB4* genes appear to be responsible for different phenotypes of EKV. There is no clear genotype-to-phenotype correlation. Yet the reported association of generalized and fixed hyperkeratoses with erythema gyratum-like red patches is not apparent in all patients with the F137L mutation affecting connexin 30.3 (Table SI; available from: http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1135) (2–4). Phenotype expression appears to be highly influenced by the individual's genetic background and environmental factors, including climate, age, and stress (1–3). We report here a case of a 44-year-old man with EKV, characterized by widespread hyperkeratoses and stable erythroderma, in whom a single base-pair transversion in the *GJB3* gene was discovered.

CASE REPORT

A 44-year-old man presented with hyperkeratoses and erythroderma. Grey-brown, verrucous, and malodorous hyperkeratoses up to 2 cm thick covered the lower half of his shanks (Fig. 1); thinner, circumscribed, but poorly demarcated, hyperkeratotic plaques were located on the back, extensor sites of the extremities, palms, and soles. The nails and scalp were unaffected. All hyperkeratoses were situated on erythematous skin. Erythroderma was stable, pronounced at the trunk and attenuated at the extremities, with some poorly demarcated small areas of normal skin. Sensorineural hearing loss was not apparent. His family history up to three generations back was negative. Having had red skin since birth, our patient was clinically diagnosed with EKV at 6 months of age and treated with topical steroids and tar ointments. At 36 years of age, the patient began a 7-year period of systemic retinoid therapy, during which the hyperkeratoses improved, but erythroderma remained unchanged. Because of arthralgias, the patient stopped using the systemic retinoids 7 months before he was seen at our department. Since then, he had not seen a physician, the hyperkeratoses had expanded again, and the malodorous smell became a problem in his job. Due to burning sensations in, and swelling of, his legs, the patient presented to our department. We treated him with topical steroids and balneotherapeutic maceration of hyperkeratoses, followed by mechanical ablation. To confirm the clinical diagnosis at the genetic level, we obtained the patient's informed consent to isolate genomic DNA from samples of his peripheral blood and search for mutations in the *GJB3* and *GJB4* genes. PCR sequence analysis revealed a mutation in the *GJB3* gene encoding connexin 31 (see Discussion).

DISCUSSION

In approximately half of patients with EKV, the causal genetic mutation has been mapped to chromosome 1p34–p35.1 (1). This locus harbours the genes *GJB3* and *GJB4* encoding connexins 31 and 30.3, respectively. These connexins belong to a family of cell membrane proteins that form gap junctions for intercellular communication. Among other functions, skin connexins provide normal keratinocyte growth and differentiation (5). At the molecular level, a mutation in connexin 30.3

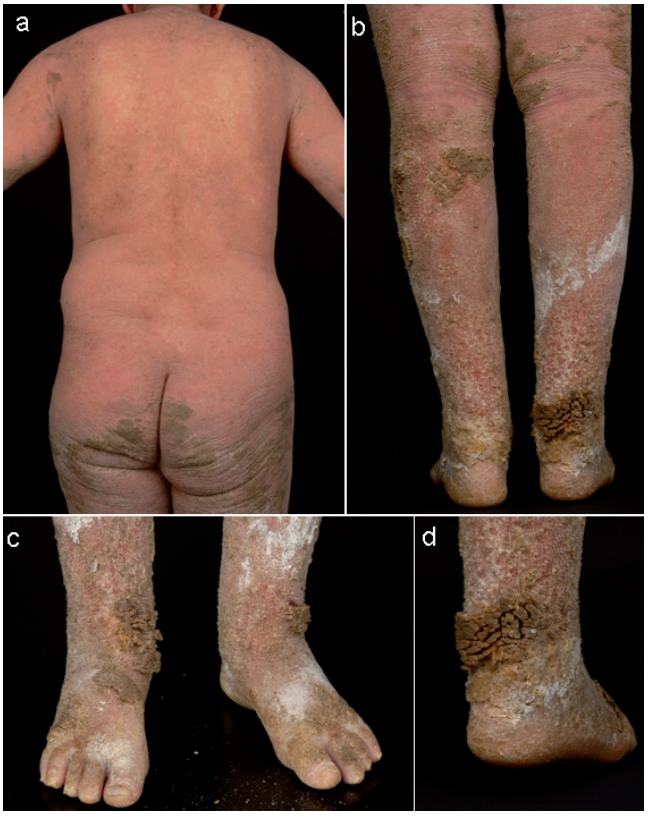

Fig. 1. Clinical appearance of a patient with erythrokeratodermia variabilis. (a) Erythematous maculae on the back with prominent hyperkeratoses on the left shoulder and buttock. (b) Prominent hyperkeratoses on erythematous skin on both legs. (c and d) Verrucous and malodorous hyperkeratoses on both ankles.

or 31 disrupts protein transport and intercellular communication. *In vitro* studies have shown that mutations in *GJB3* result in the accumulation of unfolded proteins in the endoplasmic reticulum, which in turn induces endoplasmic reticulum stress and leads to increased cell death and keratinocyte hyperproliferation (6).

To date, a variety of pathogenic mutations affecting *GJB3* and *GJB4* have been identified in families or individuals with EKV. There is considerable clinical variability, not only between different mutations, but also between individuals carrying the same mutation (Table SI). The mutation in the present patient comprises a heterozygous transversion from cytosine to adenine at position 411 (c.411C>A) in the cDNA sequence of the *GJB3* gene (Fig. S1; available from: http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1135).

This nucleotide substitution in the *GJB3* gene has not been described before. However, as previously reported, it causes an amino acid exchange from phenylalanine to leucine at position 137 in the third transmembrane domain of connexin 31 (p.Phe137Leu, F137L) (2). This amino acid exchange occasionally leads to a phenotype of pronounced hyperkeratoses, as in our patient. Furthermore, it can cause erythema gyratum repens-like skin lesions (1).

Previous reports of patients with mutations in *GJB3* and *GJB4* most often describe well-demarcated, variable, and short-lasting erythematous patches (2, 3, 7), and in some cases unaffected palms and soles (1). In contrast, the erythroderma in our patient remained stable and unaffected during retinoid therapy, and his palms and soles were hyperkeratotic.

This implies that, besides the type of mutation, the phenotype of an individual patient is strongly influenced by other genetic, epigenetic, and environmental factors (7). In a mouse model, the F137L mutation had little phenotypic expression other than small hyperkeratoses at the tail (8). In humans, by contrast, the phenotype is mostly a dominant trait. Two immediate reasons for this difference come to mind. First, the function of murine connexin 31 differs from that of the human protein. Secondly, other genetic and epigenetic factors may influence the human phenotype.

Genetic origins aside, the therapeutic opportunities for EKV are limited and usually comprise systemic retinoids (5). Retinoids enhance the normal differentiation of keratinocytes, probably due to increased production of connexin 43 thereby compensating for deficiency in connexin 30.3 or 31 (5).

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The authors declare no conflict of interest.

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