A heterozygous mutation in *GJA1* gene in Chinese family with serious erythrokeratodermia variabilis et progressive

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To the Editor: Erythrokeratodermia variabilis (EKV; MIM 133200) is characterized by the coexistence of transient, figurate, erythematous patches, and localized keratotic hyperkeratosis. EKV shows marked phenotypic heterogeneity, even within kindreds bearing the same disease-causing mutation.[1] The term EKV et progressiva (EKVP) is a severe variant of EKV and has been proposed to encompass the diversity of phenotypes, ranging from limited hyperkeratotic plaques and erythematous patches to severe progressive symmetric erythrokeratodermia which can feature more generalized cutaneous involvement.[2]

Here, we reported a Chinese family of EKVP with autosomal dominant inheritance [Figure 1A]. The proband was a 27-year-old man (III1) in this family; the patient reported there was no obvious cause and there was a clear erythema in the palms and soles of the feet at 1 month of birth, surrounded by a small piece of scale with no discomfort. With the increase of age, lesions gradually increased and spread range expanded; he was diagnosed with generalized verrucous epidermal nevus, EKV, autosomal dominant congenital ichthyosiform erythroderma, and progressive symmetrical erythrokeratodermia in different hospitals [Figure 1C–F]. Cod-liver oil, urea cream, and Vitamin E cream were used on his all lesions, but the lesions were not improved obviously. No other abnormalities were observed in nail, mucosa in oral cavity, tooth, and hair. His parents were non-consanguineous, and the patient was their first boy and he had a full-term delivery. Skin section circumstance revealed that the whole body was dry and the skin lesions were observed in palms, feet, legs, arms, elbows, thighs, and hips. The lesions showed clear border erythema with thick scales and crusts on the lesions and margins which could be peeled. Laboratory examination reported that blood, urine, stool routine, erythrocyte sedimentation rate, liver function, and renal function were normal. Auxiliary examination showed that electrocardiography and chest X-ray were normal. Histologic characteristics marked hyperkeratosis, granular-layer hypertrophy, and acanthosis, with lymphocytic infiltration around the superficial blood vessels [Figure 1G, H]. His father also had a similar clinical presentation [Figure 1K–N].

We carried out sequencing studies to find out the pathogenic gene of this family. This study was approved by the ethics committee of Anhui Medical University and conducted according to the principles of the *Declaration of Helsinki*. After obtaining informed consent from all the participants, ethylenediaminetetraacetic acid anticoagulated venous blood samples were collected from all participants. Genomic DNA was extracted from peripheral blood lymphocytes by standard procedures using TIANamp Genomic DNA Kit (TIANGEN Co., Beijing, China).

At first, we thought he and his father were suffering from autosomal dominant congenital ichthyosiform erythroderma, and we assessed the *KRT1* and *KRT10* genes in blood and tissue, but did not identify any potential mutations that in the coding regions or splice sites of these two genes which could lead to autosomal dominant congenital ichthyosiform erythroderma.

To further confirm the diagnosis and identify the causative gene, we performed next-generation sequencing using SeqCap EZ Med exome enrichment kit (Roche NimbleGen Inc., Madison, WI, USA) containing 541 genodermatosis-related genes. We identified a missense mutation in *GJA1*

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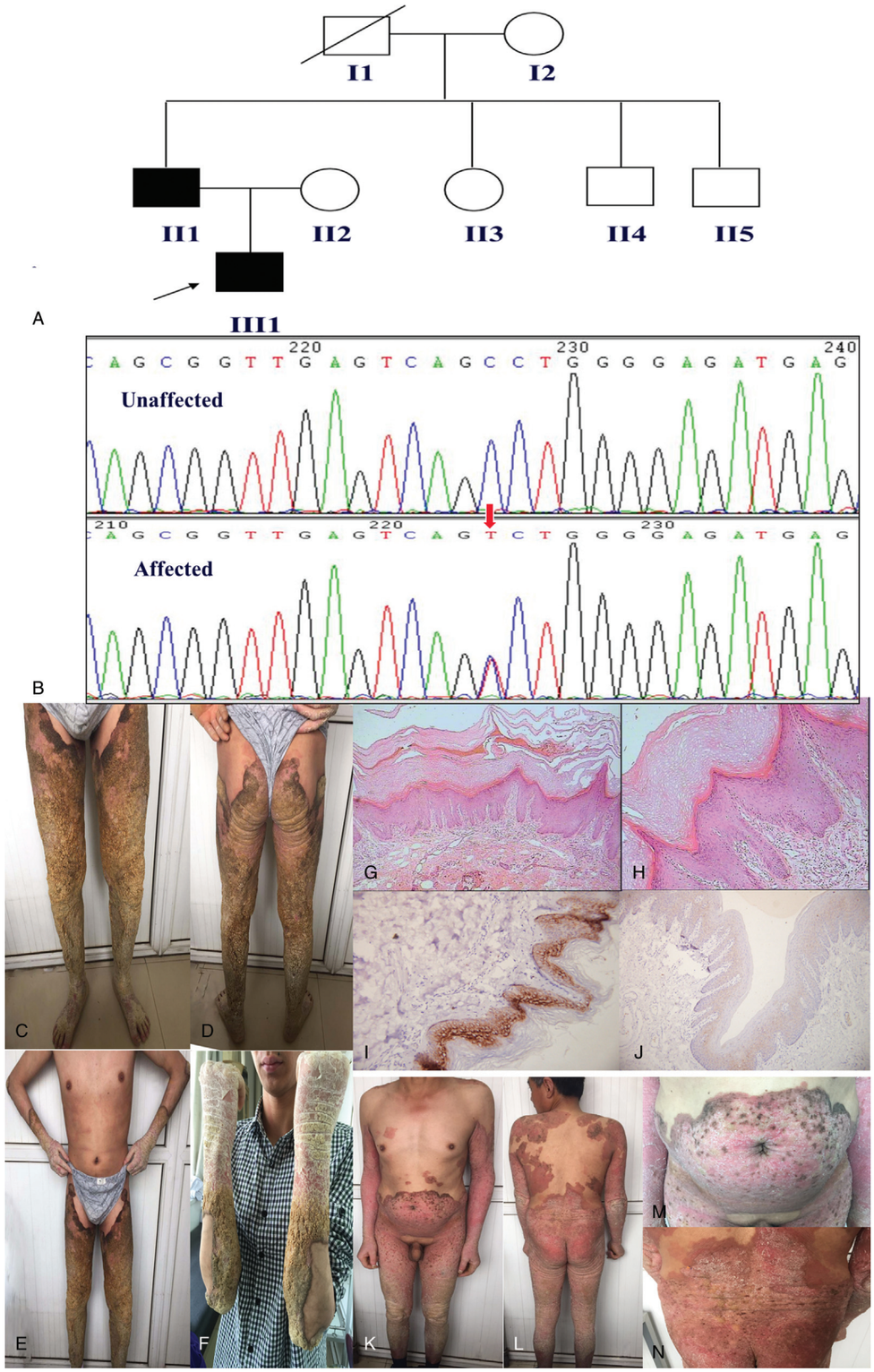

Figure 1: (A) The genealogic tree of this family: black squares indicate affected family members, and an arrow indicates the proband (III1). (B) Sanger sequencing revealed a heterozygous mutation in *GJA1* (NM_000165; CCDS5123.1: exon2: c.131C→T: p.A44V). (C, D) The lower extremity lesions of the proband. (E) The front skin lesions of the proband. (F) The forearm lesion of the proband. (G, H) Histologic characteristics: marked hyperkeratosis, granular-layer hypertrophy, and acanthosis, with lymphocytic infiltration around the superficial blood vessels (H&E staining; G: original magnification × 40, H: original mgnification × 100). (I, J) Immunohistochemistry: strong positive expression of connexin 43 (Cx43; *GJA1*; 121014) in the epidermis of the patient, and negative and weak expression in the epidermis of the control by immunohistochemistry (original magnification ×40). (K) The front skin of the proband's father. (L) The back skin of the proband's father. (M) The abdominal skin lesion of the proband's father. (N) The hips skin lesion the proband's father.

in blood of the proband (gap junction protein alpha 1) (NM_000165; CCDS5123.1: exon2: c.131C→T: p. A44V). We selected *GJA1* as the candidate causal gene for further validation analysis using Sanger sequencing. We also sequenced *GJA1* in tissue of the proband and blood of his father and identified the same missense mutation, but not in unaffected individuals in his family [Figure 1B]. In addition, we also sequenced the mutation in additional 200 unrelated, ethnically and geographically matched healthy controls and found that the mutation was also absent in these additional 200 subjects. Additionally, this mutation was predicted to be "pathogenic" by software, A44 is highly conserved in orthologs. As a result, we confirm the diagnosis of EKVP by gene diagnosis and identify *GJA1* as the causative gene of the disease about this family. It was found that strong positive expression of connexin 43 (Cx43; *GJA1*; 121014) in the epidermis of the patient, and negative and weak expression in the epidermis of the control by immunohistochemistry [Figure 1I, J].

The EKVP is a rare, inherited skin disease characterized by transient figurate patches of erythema, localized or generalized scaling, and frequent palmoplantar keratoderma.[1] Mutations in genes *GJB3*, *GJB4*, and *GJA1*,[3,4] encoding connexins 31, 30.3, and 43, respectively, have been reported to cause EKVP, though there is evidence of further genetic heterogeneity.[3] In an EKVP case, the *GJA1* p.A44V mutation was reported to show figurate erythema with a burning sensation, which led to prominent, thickened scaly skin, hyperpigmentation, and palmoplantar keratosis, which is consistent with our discovery.[3] However, in the previously reported article, their patients were sporadic, unlike what we have studied is a family, and the clinical manifestation of our patients is more serious.[3]-*GJA1* encodes a gap junction protein Cx43 which is ubiquitously expressed in various organs, including the epidermis and hair follicles.[5] In conclusion, in this study, EKVP was confirmed in this family by genetic diagnosis, and a missense mutation in *GJA1* was confirmed again.

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Conflicts of interest

The authors report no conflicts of interest.

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