hair length and thickness. Thirdly, the primary defect giving rise to Laron syndrome is a block of growth hormone signalling (Laron, 2002). Thus, some abnormalities might be not owing to IGF-I deficiency. As growth factors share many intracellular signalling pathways, a partial compensation of such defects by IGF-I treatment might be possible. Consequently, interpretation of data on Laron syndrome has to be very cautious with respect to IGF-I's role in human hair follicles. Although similarities regarding IGF-I and hair production are apparent between man and mouse, a detailed comparative analysis is still missing.

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Identification of a Novel Locus for Progressive Symmetric Erythrokeratodermia to a 19.02-cM Interval at 21q11.2–21q21.2

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TO THE EDITOR

The erythrokeratodermas (EKs) include a clinically and genetically heterogeneous group of disorders characterized by erythematous and hyperkeratotic lesions, either stationary or migratory. Two major subtypes have been defined: erythrokeratodermia variabilis (EKV, OMIM 133200) and progressive symmetric erythrokeratodermia (PSEK, OMIM 602036). PSEK is characterized by fixed erythematous keratotic plaques distributing symmetrically over the body, particularly on the extremities, the buttocks, and the faces, sometimes together with palmoplantar keratoderma. Two sisters have been described, in which the younger one suffering EKV whereas the older one suffering PSEK, and this report brought forward the hypothesis that PSEK and EKV were different manifestations of a single conditions (MacFarlane *et al.*, 1991). However, accumulating genetic studies supported the distinct molecular pathology underlying them (Richard *et al.*, 1998, 2002, 2003). The major clinical feature distinguishing between PSEK and EKV is the sharply outlined geographical regions of migratory erythema in the latter (Ishida-Yamamoto *et al.*, 1997), and parakeratosis is an evident pathological feature in PSEK and usually not seen in EKV. Furthermore, ichthyotic variant of Vohwinkel syndrome, KID syndrome, and some transgradient forms of palmoplantar keratoderma should also be differentiated from PSEK based on the clinical and histological characteristics.

The pathologic mechanism of PSEK is still unknown. No loci for PSEK have been defined by genetic linkage analysis up to date. A frameshift mutation (709insC) in the loricrin gene (OMIM #152445) on chromosome 1q21 has been identified in a Japanese PSEK family with generalized, well-demarcated erythematous hyperkeratotic plaques and mutilating palmoplantar keratoderma (pseudoainhum) (Ishida-Yamamoto *et al.*, 1997). Loricrin is a major structural component of the crosslinked cell envelope of the epidermis, which participates in the formation of keratohyalin granules (Hohl *et al.*, 1991; Candi *et al.*, 1995), and the responsibility of the loricrin gene for variant form of Vohwinkel syndrome has been demonstrated (Maestrini *et al.*, 1996). Some authors considered the Japanese pedigree mentioned above affecting variant form of Vohwinkel syndrome rather than PSEK, because pseudoainhum was usually not seen in PSEK, and the location of above mutation was only 21 bp upstream to that of Vohwinkel syndrome variant form (730insG) (Richard *et al.*, 2002). Our previous study has excluded the loricrin gene is the responsibility gene for PSEK (Cui *et al.*, 2004).

To map the disease locus of PSEK, we carried out a genome-wide scan in a five-generation Chinese PSEK family consisting of 27 individuals. There are 12 affected individuals in this family,

Abbreviations: EK, erythrokeratoderma; EKV, erythrokeratodermia variabilis; PSEK, progressive symmetric erythrokeratodermia

including five males and seven females. Kindred examined exhibited the hallmarks of autosomal dominant inheritance with high penetrance. The proband (IV:5) was a 16-year-old female, her lesions developed when she was 3 years old and did not change much thereafter. Physical examination shows well-demarcated, slightly raised, hyperkeratotic erythematous plaques distributed on the dorsum of hands and feet symmetrically, accompany with obviously palmoplantar keratoderma. Clinical and histological features are showed in Figure 1a–c. All patients have typical features of the PSEK trait, with normal mucous membranes, nails, teeth, and hair. None patient shows pseudoainhum.

This study was adherent to the Declaration of Helsinki Principles and approved by the medical ethical committee of the Anhui Medical University. After obtaining informed consent, 18 members of this family (nine affected and nine unaffected individuals) participated in this genetic study by donating 10 ml of blood for DNA extraction and genotyping analysis. Genomic DNAs were extracted from peripheral blood by use of a blood kit (Qiagen Inc., Hilden, Germany). We first undertook a genome-wide scan using 382 microsatellite markers from the ABI's Prism Linkage Mapping Set (Version 2). All the markers were genotyped in multiplex PCR following the guidelines from the manufacturer (Applied Biosystems, Foster City, CA). The results of two-point linkage analysis strongly suggest linkage at 21q11.2–21q21.2 with LOD scores of 2.82 at D21S1914 ($\theta = 0.00$). We then selected 12 additional microsatellite markers from David Duffy's interpolated map (http://www2.qimr.edu.au/davidD/), and the linkage results from these added markers confirmed our original finding by giving a maximum two-point LOD score of 4.33 at marker D21S1257 ($\theta = 0.00$). All the

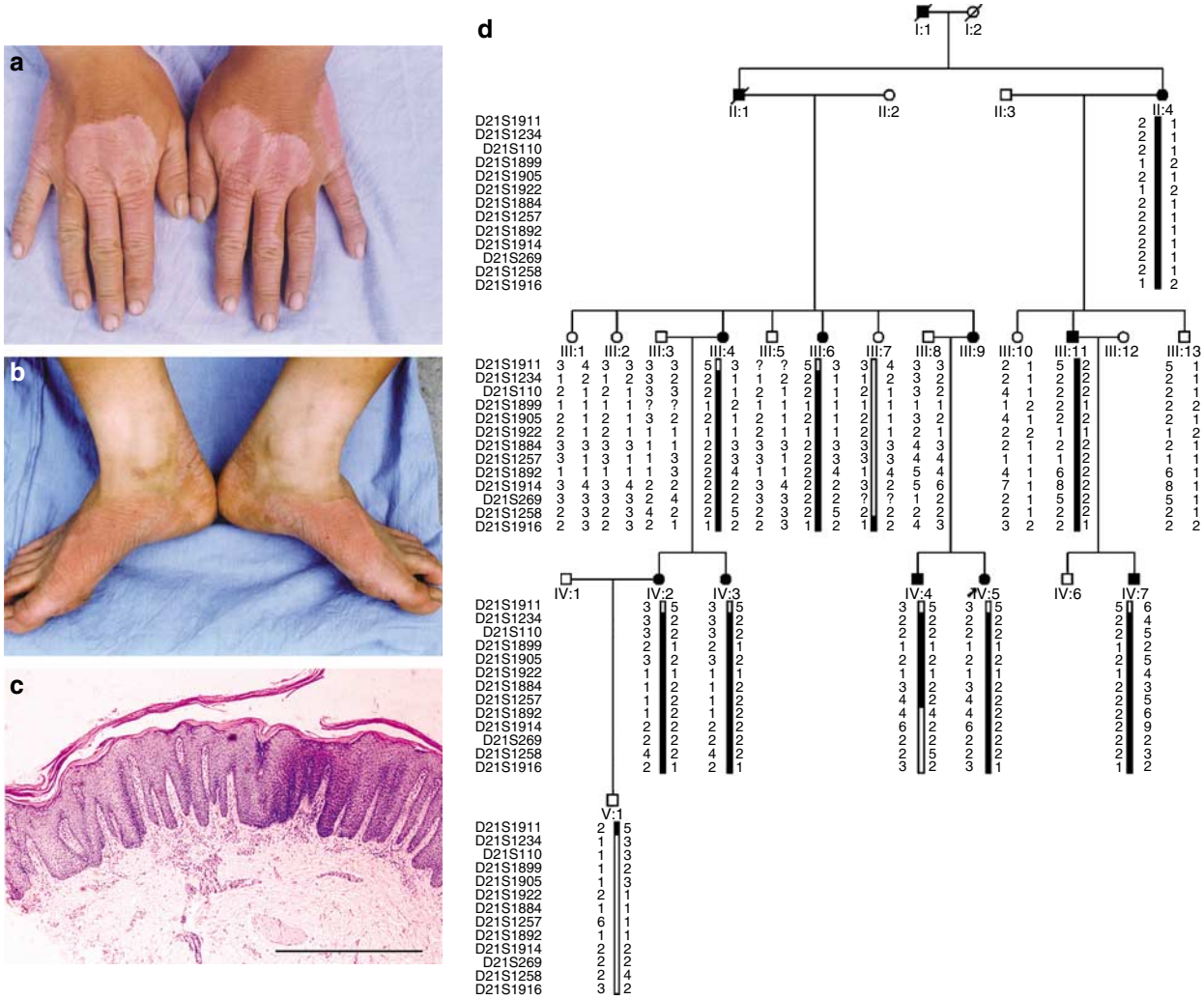

Figure 1. Clinical features and haplotype analysis of this family. (**a**) Hyperkeratotic erythematous plaques on the dorsum of hands. (**b**) Hyperkeratotic erythematous plaques on the dorsum of feet. (**c**) Histological results showing marked hyperkeratosis and parakeratosis (hematoxylin and eosin; bar = 1 mm). (**d**) Haplotype analysis of this family: Black symbols denote affected individuals, while white symbols denote unaffected individuals. Haplotypes are shown for all available members with marker names at the left of each generation. Black bars represent disease-carrying haplotypes, and the gray bar denotes noninformative regions adjacent to critical recombination events. The black arrow indicates the proband of this family.

Table 1. Two-point linkage analysis between PSEK and the markers at chromosome 21

		LOD score at θ				
Markers	**Location (cM)**	**0.00**	**0.10**	**0.20**	**0.30**	**0.40**
D21S1911	3.60	*−4.34*	0.39	0.62	0.43	0.08
D21S1234	5.83	1.64	1.25	0.84	0.44	0.13
D21S110	9.29	1.79	1.38	0.95	0.51	0.15
D21S1899	13.60	0.12	0.06	−0.01	−0.05	−0.04
D21S1905	15.44	1.77	1.37	0.94	0.50	0.15
D21S1922	17.92	2.18	1.75	1.29	0.79	0.28
D21S1884	18.58	3.92	3.20	2.41	1.54	0.62
D21S1257	21.79	4.33	3.53	2.67	1.71	0.69
D21S1892	22.62	1.05	2.41	2.00	1.37	0.61
D21S1914	23.30	2.82	2.29	1.70	1.07	0.42
D21S269	26.62	2.71	2.18	1.62	1.01	0.39
D21S1258	28.71	*−1.06*	0.63	0.58	0.40	0.09
D21S1916	29.05	*−2.50*	0.89	0.84	0.53	0.19

LOD scores were calculated under an autosomal dominant mode of inheritance, a penetrance of 99.9% at various recombination fractions. Genetic coordinates in centimorgans according to David Duffy's interpolated map.

two-point LOD scores of the 13 markers analyzed in this study were summarized in Table 1.

To determine the smallest interval containing the PSEK locus, recombination events among the family members were analyzed by haplotype reconstruction (Figure 1d). Autosomal dominant inheritance with 99.9% penetrance was assumed. The affected allele frequency was taken as 0.0001. Marker allele frequencies were obtained from all individuals' genotyping data. The recombination frequency was assumed to be equal for both sexes. Two-point linkage analysis was performed using Linkage programs version 5.10, haplotypes were constructed with Cyrillic Version 2.02 software. The recombination events in individuals III:4, III:6, IV:2, IV:3, IV:4, IV:5, IV:7, and V:1 place the PSEK locus upper to D21S1911 and an affected members (IV:4) place the lower boundaries to D21S1892. These results suggest that the gene responsible for PSEK in this family lies in the 19.02 cM interval between D21S1911 and D21S1892.

This interval spans about 9 Mb on the physical map. There are 23 genes within the critical regions, including 18 confirmed genes. Four known genes (NRIP1 (OMIM 602490), USP25 (OMIM604736), BTG3 (OMIM 605674), and CHODL (OMIM 607247)), whose transcripts had been isolated from skin cDNA libraries could be selected as candidate genes for further investigation. Ubiquitin, the encoded protein of USP25, is a highly conserved 76-amino-acid protein involved in the regulation of intracellular protein breakdown, cell cycle regulation, and stress response. BTG3 is a novel member of the PC3/BTG/TOB family of growth inhibitory genes. CHODL is a type I transmembrane protein homologous to C-type lectins, which characterized by calcium-dependent carbohydrate-binding activity and a common carbohydrate recognition domain. Keratin genes were considered to be good candidates because several hyperkeratotic cutaneous disorders are caused by mutations of keratins (Fuchs and Cleveland, 1998; Coulombe and Omary, 2002), but no known keratin gene was found in this locus.

In conclusion, we identified a novel locus for PSEK on chromosome 21q11.2–21q21.2 in a Chinese family. It will aid future identification of the responsible gene, which will be useful for the understanding of the molecular mechanism of PSEK.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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ELECTRONIC DATABASE INFORMATION

Mapview, http://www.ncbi.nlm.nih.gov/mapview/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/OMIM
David Duffy's QIMR Homepage, http://www2.qimr.edu.au/davidD/

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Production of Low Titers of Anti-Desmoglein 1 IgG Autoantibodies in Some Patients with Staphylococcal Scalded Skin Syndrome

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TO THE EDITOR

Staphylococcal scalded skin syndrome (SSSS) is a generalized blistering skin disease caused by *Staphylococcus aureus* producing exfoliative toxin (ET). ET is a serine protease that specifically digests desmoglein 1 (Dsg1), the autoimmune target for pemphigus foliaceus (PF). Out of 30 patients with SSSS, six (20.0%) patients developed low titers of anti-Dsg1 IgG, but no detectable anti-Dsg3 IgG, 7 days or more after the onset of the disease. Although other genetic or environmental factors are necessary for the full development of pemphigus, this finding provides evidence that infection could trigger the autoimmune reaction.

A major question in understanding the pathophysiology of autoimmune disease is what triggers the immune response. One postulated mechanism, molecular mimicry, has been that infectious agents might cause antibodies that bind self-antigens, a good example being streptococcal antigens in rheumatic heart disease (Wucherpfennig, 2001). In such cases, the antibodies that are produced against the infectious agent are thought to coincidentally crossreact with normal tissues. The recent elucidation of the pathophysiology of an antibody-mediated tissue-specific autoimmune disease, PF, and two related infectious diseases, bullous impetigo (BI) and SSSS, all of which target the same molecule, Dsg1, suggested to us another mechanism by which an infectious agent could trigger an autoimmune response. In this mechanism, we hypothesize that a bacterial toxin could bind to and partially degrade a self-antigen, with the modified self-antigen triggering the immune response.

Impetigo is the most common bacterial infection of children and 30% of these patients have BI, which is caused by *S. aureus* that produces ETs. SSSS is a generalized form of BI, which occurs in newborns, young children, and adults with renal failure and/or who are immunocompromised. In the early 1970s, ETs of two major serotypes, ETA and ETB, were shown to produce blisters in the superficial epidermis when passively transferred to neonatal mice (Melish and Glasgow, 1970). It took almost 30 years to elucidate the pathophysiological mechanism of action of ETs, which have recently been shown to be glutamate-specific serine proteases that specifically bind and cleave Dsg1 (Amagai *et al.*, 2000). Desmogleins are cadherin-type cell—cell adhesion molecules found in desmosomes and play a critical role in maintaining tissue integrity in epithelial and other tissues (Green and Gaudry, 2000).

Desmogleins are also affected in the skin autoimmune blistering disease, pemphigus (Payne *et al.*, 2004). Among four isoforms of desmoglein, Dsg1 is targeted by IgG autoantibodies in PF, which shows superficial epidermal blisters with identical histological findings to SSSS/BI. Thus, in both PF and SSSS/BI the inactivation of Dsg1 causes superficial blisters in skin.

If, as postulated above, altered antigen, in this case Dsg1, could trigger an immune response, we would expect that some patients with SSSS or BI produce at least low-level antibodies against Dsg1. To address this hypothesis, we examined a total of 58 serum samples from 30 patients with SSSS and 12 serum samples from 12 patients with BI after informed consent with

Abbreviations: BI, bullous impetigo; Dsg1, desmoglein 1; ET, exfoliative toxin; PF, pemphigus foliaceus; SSSS, staphylococcal scalded skin syndrome