Ethnic variations in IRS keratins alter the interaction between the keratins

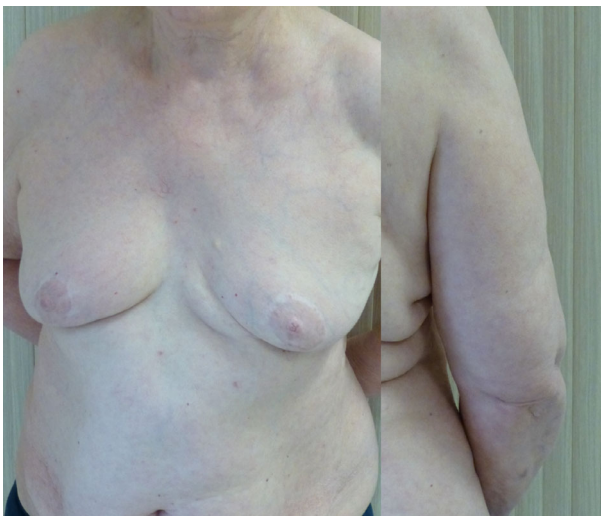

Figure 2 Resolution of clinical lesions with ustekinumab treatment

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Ethnic variations in IRS keratins alter the interaction between the keratins

Dear Editor,

Hair shape is one of the most evident features presenting ethnic difference in skin and hair. Among the Asian and Caucasian populations, straight and wavy hair are dominant; in contrast, most Africans have tightly curved curly to coiled hair.[1] So far, various mechanisms determining hair shape have been indicated. Thibaut *et al*.[2] have shown that asymmetry in hair bulb and mechanical stress is one of the key phenomena for hair shape. By a genome-wide association study in Caucasians, the variations in *TCHH* gene expression in the inner root sheath (IRS) of the hair were reported as one of the genes determining the hair shape.[3] In addition, we previously reported that the structural disparity in IRS is caused by the porous, uneven distribution pattern of IRS keratins, which is one of the key characters for curly hair shape.[4] Regarding the IRS keratin genes, several mutations were reported in the disease presenting woolly hair.[5] Thus, the role of the IRS keratin genes is thought to be very important in determination of hair shape. In the Hap-Map database, the ethnic variations in IRS keratin genes (type I *KRT25* and type II *KRT71*) were reported in the coding region following missense mutations. In the *KRT25* gene, T allele is dominant in Asians and Caucasians at the 222nd position of the cDNA, and in contrast, the C allele is dominant in individuals of African descent, which causes amino acid variation Leu to Ser at the 54th position in the head domain of its protein (Fig. 1a). Similarly, the variations from C allele (Asian and Caucasian) to T allele is found at the 1461st position casing alteration of Gly to Val at the 464th amino acid in the tail domain of K71 (Fig. 1b). We confirmed those variations by sequencing the pooled scalp cDNAs from Asian/Caucasian and African people. Then, we examined the effect of those ethnic variations in K25 and K71 keratins on the protein-protein interaction by commercially available mammalian two hybrid system using VP16 and Gal4-DNA-BD (Promega). The expression of VP16-K25 and Gal4-DNA-BD-K71 fusion proteins from Asian/Caucasian and African individuals were confirmed by the transfection to HEK293A cells (Fig. 1c). Using HEK293A cells transfected with VP16-K25 and Gal4-DNA-BD-K71, the

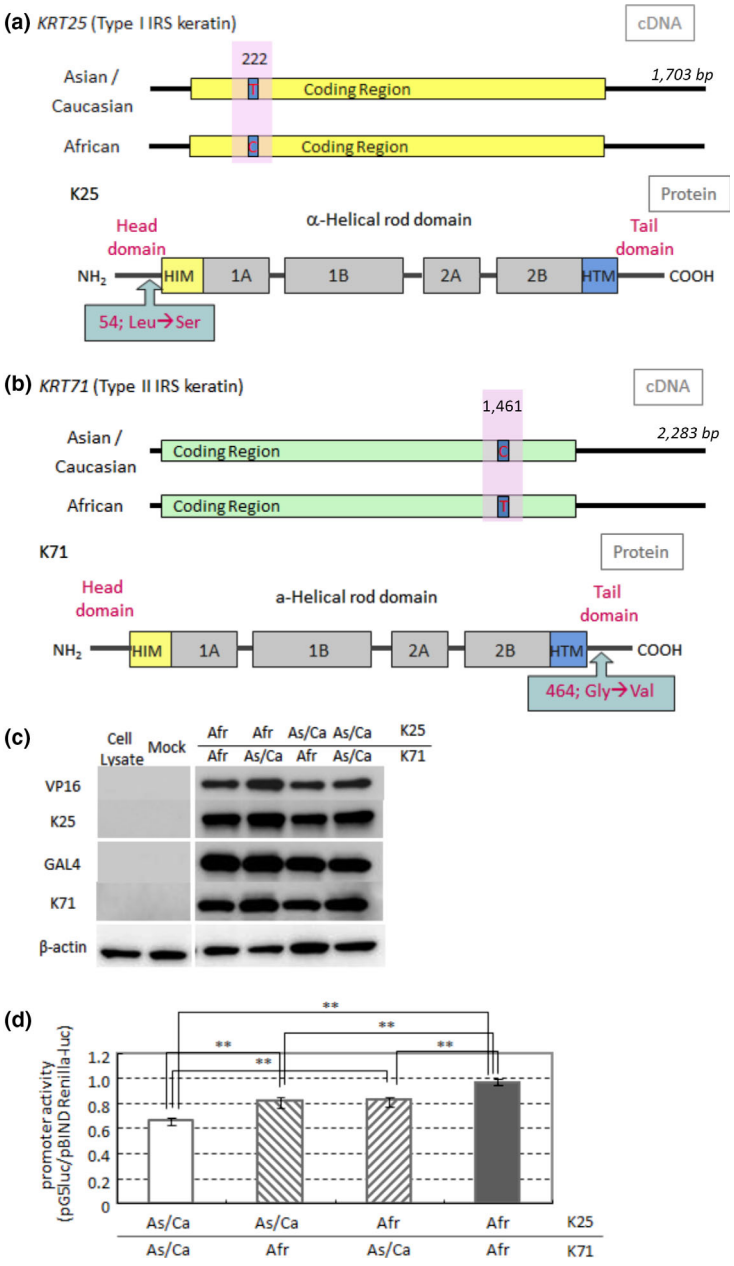

Figure 1 (a) A difference in the sequence of type I IRS keratin *KRT25* cDNA and K25 proteins between Asian/Caucasian and African populations. The allele frequency of SNPs at the 222 position of *KRT25* cDNA (rs12951399) is C = 0.58672 T = 0.41328 for European, C = 0.5549 T = 0.4451 for East Asian and C = 0.9209 T = 0.0791 for African from the result of the genome Aggregation Database. (https://www.ncbi.nlm.nih.gov/snp/rs12951399#frequency_tab) HIM and HTM mean helix initiation motif and helix termination motif, respectively. (b) The ethnic difference in the sequence of type II IRS keratin *KRT71* cDNA and K71 proteins between Asian/Caucasian and African individuals. The allele frequency of SNPs at the 1461 position of *KRT71* cDNA (rs10783518) is T = 0.5109 C = 0.4891 for European, T = 0.476 C = 0.524 for East Asian and T = 0.903 C = 0.097 for African from the result of the genome Aggregation Database. (https://www.ncbi.nlm.nih.gov/snp/rs10783518#frequency_tab) (c) Western blot analysis of VP16-K25 and Gal4-DNA-BD-K71 transiently transfected into HEK293A cells. As/Ca: Asian/Caucasian, Afr: African. The following primary antibodies were used in Western blotting. The anti-K25 and anti-K71 antibodies were the gift from Dr. L. Langbein (*J. Invest. Dermatol.* 126, 2377–2386), anti-GAL4(DBD) (RK5C1) from Santa Cruz, anti-VP16 (SC-7546) from Santa Cruz and anti-β-actin (#4970) from Cell Signaling Technology (d) The strength of the interaction between K25 and K71 proteins examined by the reporter gene assay in HEK293A transfected with expression vectors coding proteins of each ethnic population. **Mean $P < 0.01$ by Bonferroni/Dunn's test

reporter gene assays were performed for examining the strength of type I and type II keratins interaction. As a result, the interaction between African K25 and K71 proteins showed approximately 1.5-fold stronger than that of Asian/Caucasian proteins. When we combined the K25 and K71 from different ethnic origins, the strength of their interaction was the intermediate value (Fig. 1d).

Next, the effect of those ethnic variations in IRS keratins was examined in the formation of keratin filaments by transiently transfecting those proteins in PtK2 epithelial cells (Fig. 2). When the African type of both K25 and K71 proteins were introduced, the keratin filaments composed with transfected IRS keratins showed aggregation as it was seen transfected cells with K25 from woolly hair.[5] In contrast, keratins of Asian/Caucasian showed uniform distribution over the cell. In the combination of IRS keratins from the different origin, type II keratin K71 seemed to affect more dominantly than type I keratin K25. Taken together, we have shown that the ethnic variations not existing in alpha-helical rod domain in IRS keratins affect the formation of keratin bundles, which was in parallel with the phenomena that we detected in situ IRS of the hair follicle from each race. Although a detailed mechanism on how the difference in the

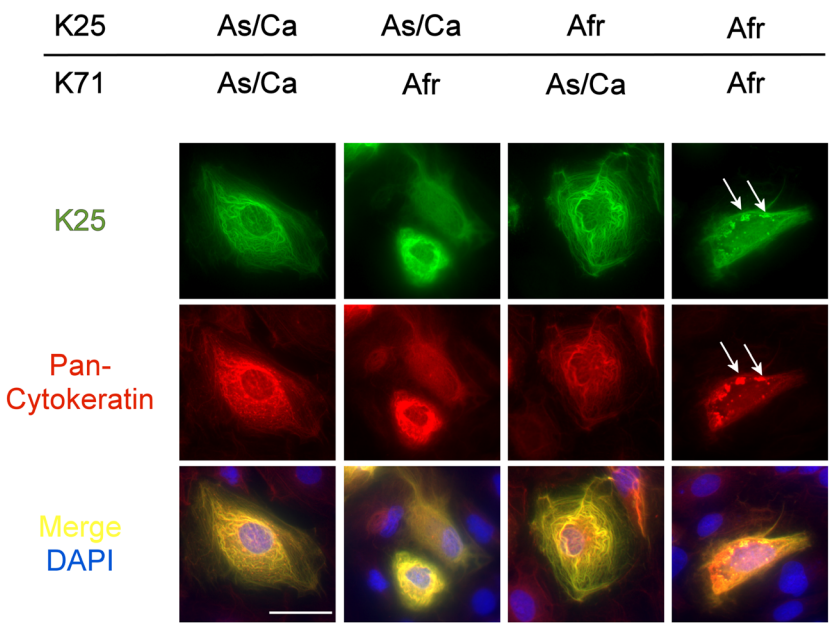

Figure 2 Immunofluorescence of PtK2 rat kangaroo epithelial cells presented that the transfection of African K25 and K71 showed aggregation of keratin filaments. Arrows identify the areas of highly aggregated keratin filaments. The following primary antibodies were used for immune-fluorescence: guinea pig anti-K25 antibody gift from Dr. L. Langbein (*J. Invest. Dermatol.* 126, 2377–2386), mouse anti-Pancytokeratin (AE1/AE3, Dako). Then, Cy-3-labeled anti-mouse IgG (Jackson Immuno-research) and Alexa-488-labeled anti-guinea pig IgG (Invitrogen) were used as secondary antibodies. As/Ca, Asian/Caucasian; Afr, African. Scale bar = 40 μm

single amino acid residue in K25 and K71 affects their structural conformation is still unclear, IRS and keratins in IRS have crucial roles in determining human hair shape by nature.

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Dermoscopy and pathological correlation of microcystic cutaneous lymphatic malformation: a rare cutaneous entity

Dear Editor,

A 24-year old Caucasian woman presented to our Institute with a 5-month history of an asymptomatic, 5 × 4 mm translucent vesiculopapular lesion in her left abdomen. Dermoscopy showed a yellowish background with peripheral linear ectatic vessels (Fig. 1). On both clinical and dermoscopic examination, a clear liquid content of the lesion was evident.

Histology showed dilated thin-walled lymphatic vessels, in the papillary dermis, lined by a single layer of flattened endothelial cells positive for CD34, CD10, focally positive for podoplanin D2-40, negative for epithelial markers and WT-1 (Figs. 2a–d). The lumen was empty. A discrete lymphocytic inflammatory infiltrate was present in the wall of the vessels. A final diagnosis of microcystic cutaneous lymphatic malformation (MCLM), previously known as lymphangioma circumscriptum (CLC), was made.

Cutaneous lymphangiomas (CL) are uncommon cutaneous lesions, accounting for 4% of all vascular tumors.[1] CL are usually congenital, although they may appear spontaneously in