Novel mutations in *SASH1* associated with dyschromatosis universalis hereditaria

Sir,

Dyschromatosis universalis hereditaria is a group of congenital pigmentary disorders characterized by generalized mottled hypopigmented and hyperpigmented macules.[1] It clinically overlaps with dyschromatosis symmetrica hereditaria and Dowling–Degos disease and genetically shows heterogeneity with at least two causative genes reported, viz., *ABCB6* and *SASH1*.[1,2] Here, we present two Chinese families with dyschromatosis universalis hereditaria and report two novel missense mutations in *SASH1* gene.

Two Chinese families with autosomal-dominant dyschromatosis universalis hereditaria were referred to our outpatient clinics [Figure 1a and b]. Proband 1 was a 25-year-old woman born with normal skin pigmentation. At the age of 3 years, freckle-like macules appeared initially on her trunk, and then gradually extended to involve her face, neck and limbs with accentuation on sun-exposure areas. Hypopigmented patches were also noted on these areas intermingled with hyperpigmentation [Figure 1c and d]. She was otherwise healthy. Her mother and deceased maternal grandfather had similar phenotypes. Proband 2 was a 42-year-old man who experienced a similar clinical process to that of the proband 1 but with an earlier onset at 7 months after birth. The dyschromatosis gradually progressed with age and involved nearly the whole body at the age of 7 years with sparing of the palmoplantar and mucosal areas [Figure 1e–g]. Affected family members showed similar clinical manifestations and were otherwise healthy.

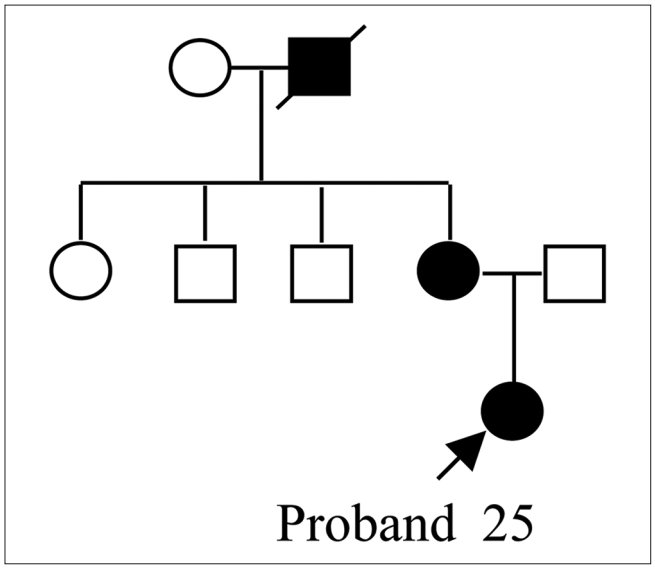

Figure 1a: Pedigrees of the first family

Following informed consent and approval from Clinical Research Ethics Committee of Peking University First Hospital, genomic DNA from the two probands were screened for mutations in the coding exons and their flanking sequences of *ADAR*, *ABCB6* and *SASH1* genes. As a result, two novel heterozygous missense mutations, c.1784T>C (p.M595T) and c.1651T>C (p.Y551H) [Figure 2a and b], in *SASH1* were identified in probands 1 and 2, respectively. All living family members were genetically tested. The mutations segregated with the phenotype of dyschromatosis universalis hereditaria perfectly in both families. Both mutations were predicted to be "disease causing" (with

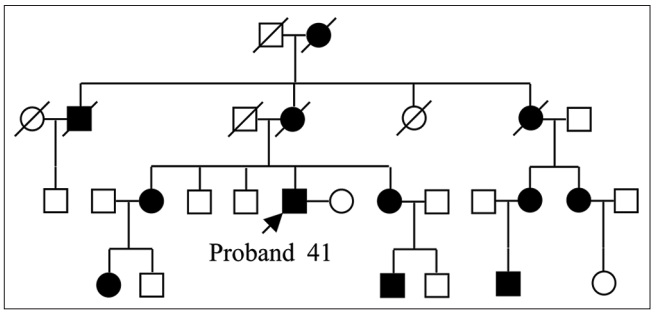

Figure 1b: Pedigrees of the second family

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a probability score of 0.999) in mutation taster (http://www.mutationtaster.org/). While M595T substitution was predicted to be "tolerated" with a score of 0.45 in SIFT (http://sift.bii.a-star.edu.sg) and "possibly damaging" with a score of 0.568 in polyphen2 (http://genetics.bwh.harvard.edu/pph2), the Y551H substitution was predicted to "affect protein function" with a score of 0.00 in SIFT and "probably damaging" with a score of 0.999 in polyphen2. Both mutated amino acids were highly conserved across different species.

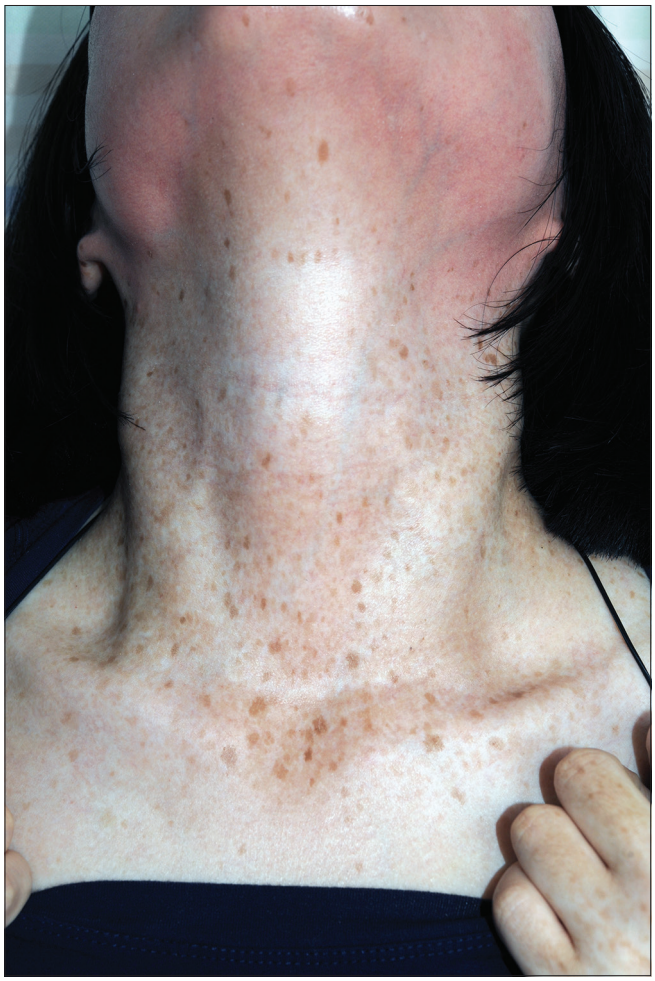

Figure 1c: Small hyperpigmented macules on the neck in proband 1

SASH1 is located on chromosome 6q24.3, and encodes a signal adaptor protein (SASH1) of 1247 amino acids that contains an evolutionarily conserved SLY domain (401-555), an SH3 domain (557-614) and two SAM domains (633-697; 1177-1241, annotation from the UniProt database) [Figure 2c]. As a potential tumor suppressor, *SASH1* gene has been reported to be involved in the tumorigenesis of lung cancer, breast cancer, colon cancer and melanoma.[3] In addition, *SASH1* has also been demonstrated to mediate skin melanogenesis through a cascade of p53/α-MSH/POMC/Gαs/SASH1.[4] As shown in Table 1, both autosomal-recessive and -dominant mutations in *SASH1* have been associated with human skin dyschromia, including dyschromatosis universalis hereditaria, multiple lentigines and pigmentation defects with palmoplantar keratoderma and skin carcinoma.[2,3] To date, seven of the eight different *SASH1* mutations identified that result in skin dyschromia are located in the highly conserved SLY domain [Figure 2c], suggesting that the SLY domain is functionally critical for skin pigmentation regulation and may represent a potential mutational hotspot region.[2,5]

Mutation p.Y551H, which is located in the SLY domain, resulted in more generalized skin lesions and an earlier onset in proband 2, compared with proband 1. An alternative residue substitution in Y551 (p.Y551D) has been reported to result in dyschromatosis universalis hereditaria in another Chinese family.[5] These data further

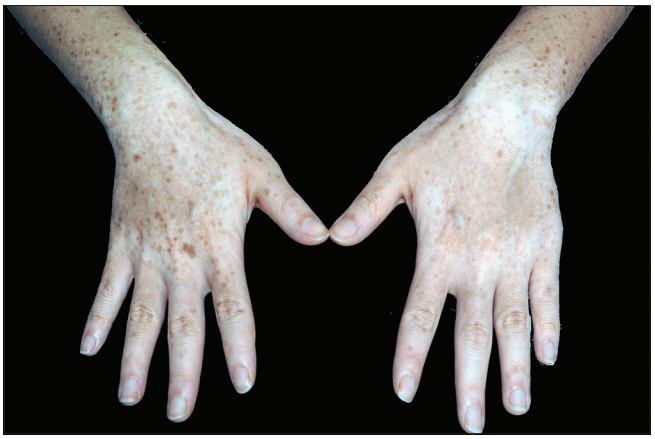

Figure 1d: Small hypo- and hyperpigmented macules on the dorsal aspects of both hands in proband 1

Table 1: Pigmentary genodermatosis and their clinical features with implicated *SASH1* mutations

Skin diseases or phenotypes	Clinical features	Mutations in *SASH1*
Dyschromatosis universalis hereditaria[2,5]	Autosomal-dominant; generalized mottled hypopigmented and hyperpigmented macules	Heterozygous mutations p.E509K, p.L515P, p.Y551D, p.Y551H*, p.M595T*
Lentiginous phenotype[2,5]	Autosomal-dominant; multiple lentigines prominent in sun-exposed areas with or without dyschromatosis	Heterozygous mutations p.S507A, p.L511Kfs*21, p.S513R, p.S519N
Lentiginous phenotype, palmoplantar keratoderma and skin carcinoma[3]	Autosomal recessive; multiple hyperpigmented macules on the trunk, face and extremities; palmoplantar keratoderma and skin carcinoma	Homozygous mutation p.E617K

**SASH1* mutations in present cases

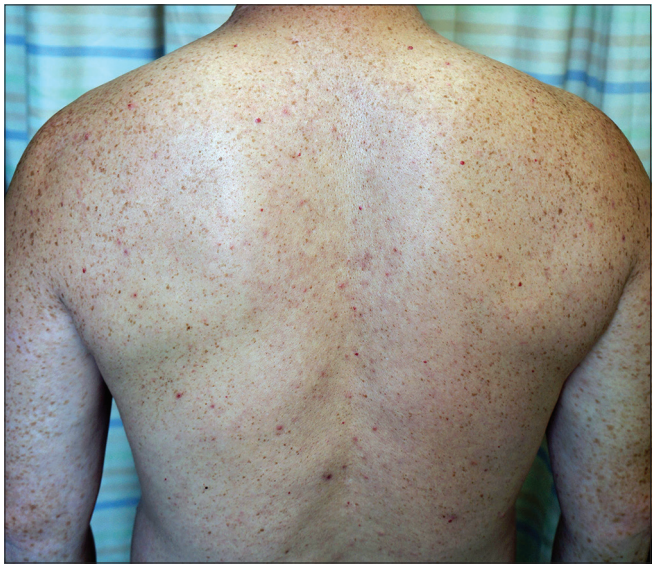

Figure 1e: Mottled hypo- and hyperpigmented macules on the back in proband 2

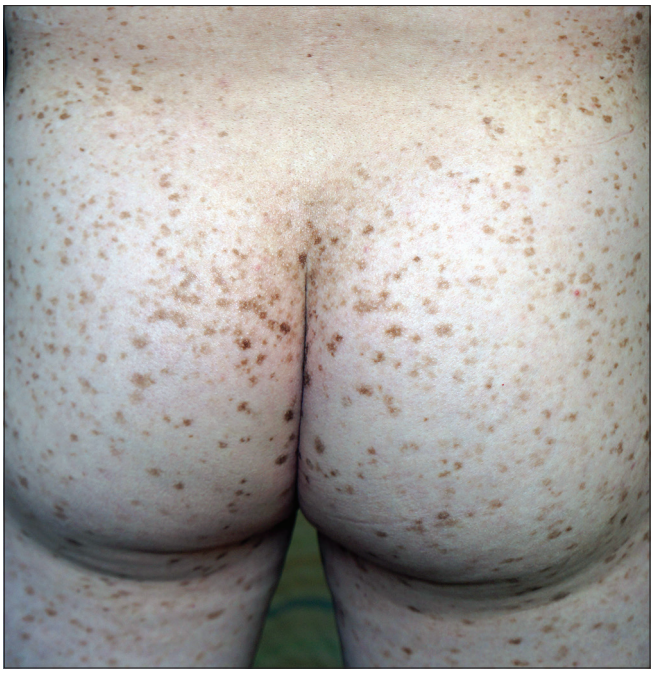

Figure 1f: Mottled hypo- and hyperpigmented macules on the hips in proband 2

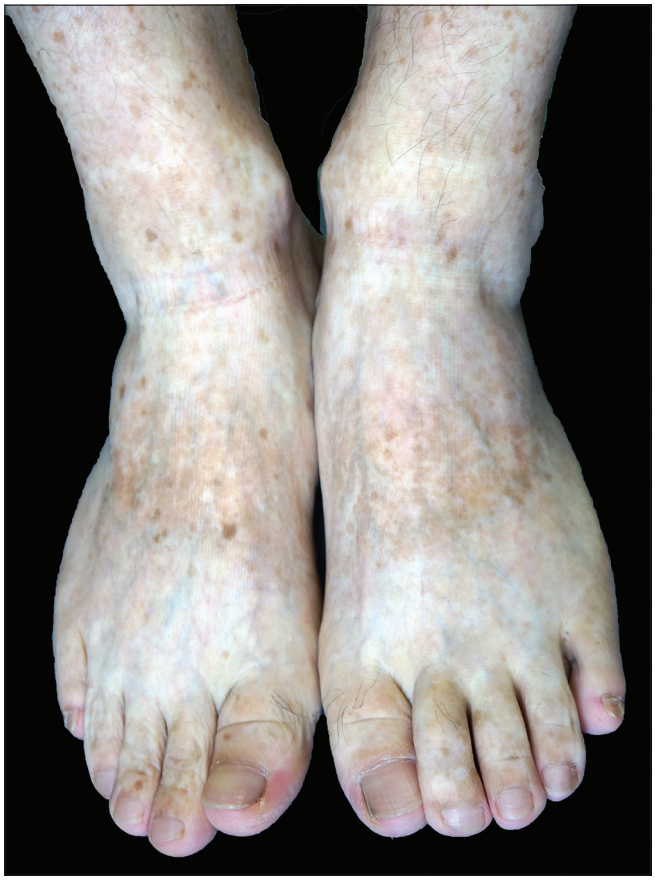

Figure 1g: Mottled hypo- and hyperpigmented macules on the dorsal aspects of both feet in proband 2

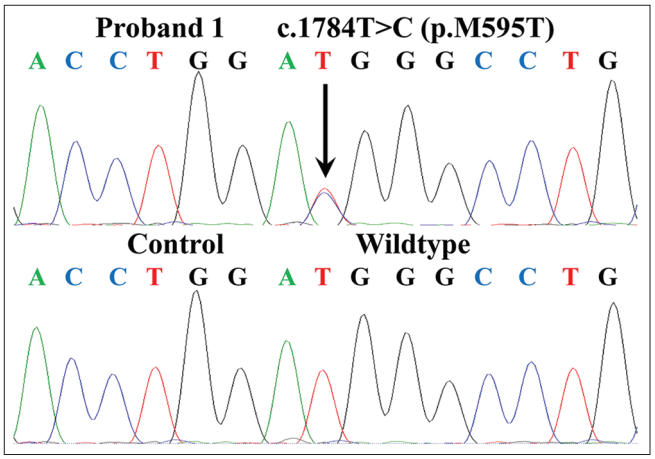

Figure 2a: Heterozygous missense *SASH1* mutation c.1784T > C (p.M595T) was identified in proband 1 (upper panel). Healthy control individuals had the wildtype sequence (lower panel)

confirm that the SLY domain is critical for mediation of melanogenesis and suggest that Y551 may be a mutation hotspot for dyschromatosis universalis hereditaria [Figure 2c].[2,5] The p.M595T is the first heterozygous missense mutation reported in the SH3 domain. SH3 domain can bind to proline-rich protein motifs and thus is critical for protein–protein interaction. It also mediates the formation of signaling complexes.[4] We infer that mutation p.M595T may impede *SASH1* interaction with other proteins and subsequent formation of signaling complexes. However, further functional studies are required to elucidate how this mutation affects the function of *SASH1*.

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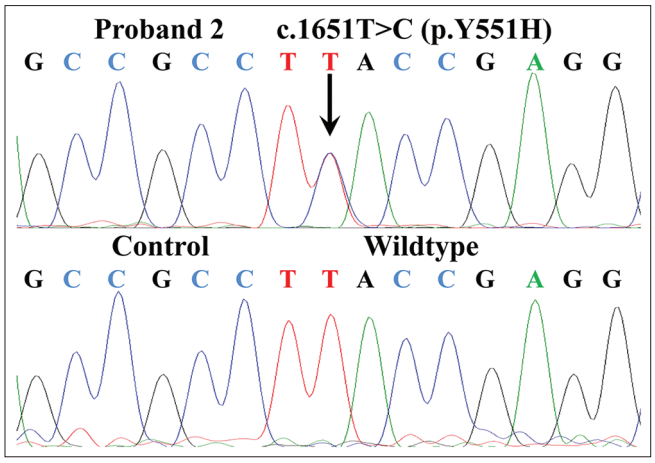

Figure 2b: Heterozygous missense *SASH1* mutations c.1651T > C (p.Y551H) was identified in proband 2 (upper panel). Healthy control individuals had the wildtype sequence (lower panel)

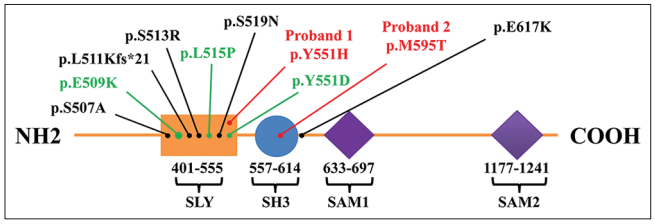

Figure 2c: Structure of the SASH1 protein, depicting the functional domains and locations of mutations. Ten mutations have been described in *SASH1*. Mutations that contributed to the dyschromatosis universalis hereditaria phenotype were marked in *green* (reported) and *red* (present cases). Mutations marked in *black* contributed to lentiginous phenotype, or with palmoplantar keratoderma and skin carcinoma

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their name and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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