Net Letter

Progressive Nagashima-type palmoplantar keratosis in a Chinese patient with recurrent c.796C>T mutation in *SERPINB7*

Sir,

Nagashima-type palmoplantar keratosis (OMIM 615598) is a mild form of diffuse, transgradient palmoplantar keratoderma which was first described in Japan.[1] Clinically, it is characterized by diffuse hyperkeratosis with erythema extending to the dorsum of hands and feet, wrists, ankles and Achilles tendon. Recently, it has been associated with loss-of-function mutations in *SERPINB7*.[2] Depletion of SERPINB7, a specific serine protease, may lead to excessive degradation of epidermal proteins resulting in enhanced water permeation of stratum corneum and consequent hyperkeratosis.[2] Herein we report a severe, progressive case of Nagashima-type palmoplantar keratosis with a recurrent homozygous mutation c.796C>T in *SERPINB7*.

The patient was a 28-year-old woman of Chinese Han ethnicity, born of a non-consanguineous marriage. She was apparently normal at birth. At 7 months of age, she was noted to have scaly erythema on the palms and soles. Thereafter, she developed diffuse reddish hyperkeratosis with scaling that gradually extended to the dorsum of her hands and feet, wrists and ankles. Notably, the condition continued to progress after puberty to involve her distal forearms, elbows, shins, knees, lower thighs and perianal area with intense pruritus [Figure 1a-c]. Leukokeratosis and fissures were found on her tongue but the rest of the buccal mucosa was spared [Figure 1d]. She also reported mild palmoplantar hyperhidrosis and had suffered repeated episodes of tinea pedis. Whitish, spongy change was observed on her palms and soles after contact with water for about 2 minutes. Her mother, too was noted to have mild thickening and redness of the palmoplantar skin extending to the marginal areas. The mother had also noticed a whitish spongy change after water exposure for 6 years, which did not progress [Figure 1e and f]. The patient and her mother were otherwise healthy and had no significant systemic illnesses other than a history of asthma and allergic rhinitis in the patient. No other family members were reported to suffer from similar symptoms.

Genomic DNA was extracted from the peripheral white blood cells for further studies after getting approval from the institutional ethics committee and informed consent from the participants. We performed the Sanger sequencing method in all coding and flanking sequences of *SERPINB7* gene in the family and detected a homozygous mutation c.796C>T (p.Arg266*) in *SERPINB7* in the patient, which was heterozygous in her mother [Figure 2] and her unaffected brother (her father was deceased, thus no DNA samples were available). In addition, mutations in 51 other genes known to be associated with inherited ichthyosis or palmoplantar keratoderma were excluded by next-generation target sequencing [Table 1].

Kubo *et al*. recently identified *SERPINB7* as the causative gene of Nagashima-type palmoplantar keratosis. They detected three different loss-of-function mutations in *SERPINB7* in 13 unrelated Japanese individuals with this condition.[2] Of note, all the patients in their study harbored a nonsense mutation c.796C>T in *SERPINB7*, either homozygous or compound heterozygous. Later, Yin *et al*. reported seven unrelated Chinese patients with this condition and identified the recurrent c.796C>T mutation in *SERPINB7* in six patients.[3] Interestingly, according to the 1000 Genomes Project, c.796C>T (rs142859678) is prevalent in the normal Japanese and Chinese population with frequencies of 1.12% and 1.52%, respectively. It is putatively the

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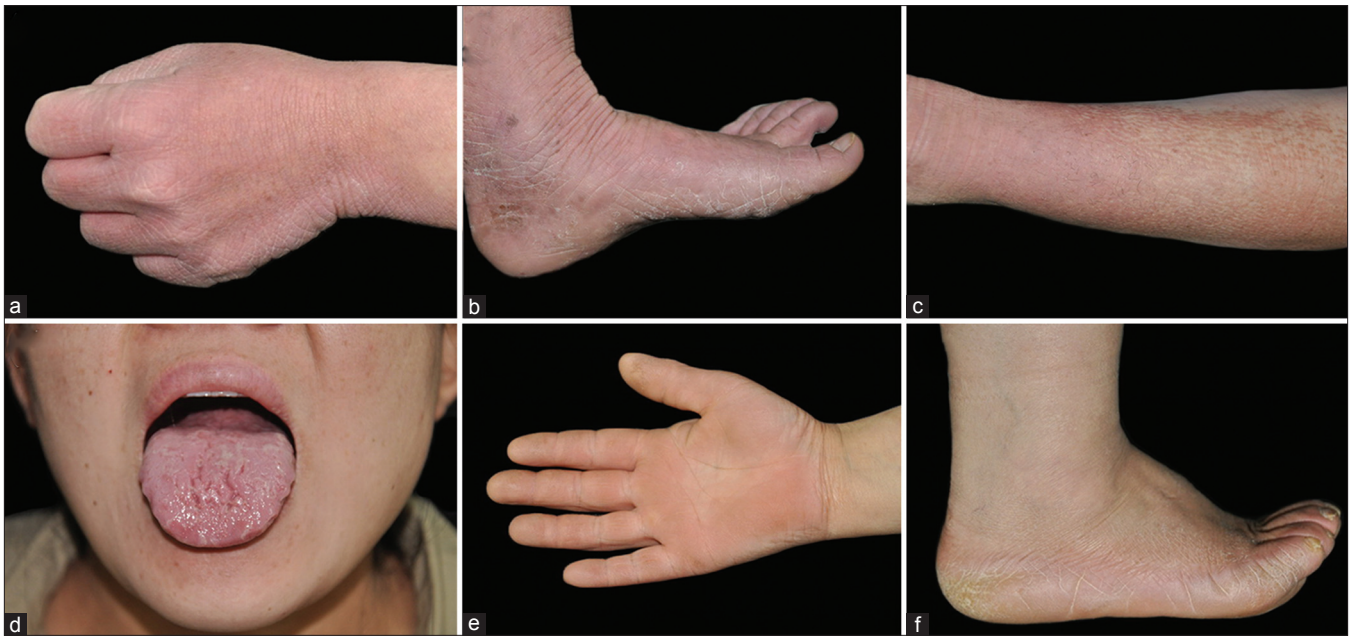

Figure 1: (a-c) Widespread reddish hyperkeratosis affecting the dorsum of the patient's palms and soles, as well as the extensor aspect of her shin. (d) Leukokeratosis and fissures on the patient's tongue. (e and f) Mild palmoplantar keratoderma extending to the margins, in the patient's mother

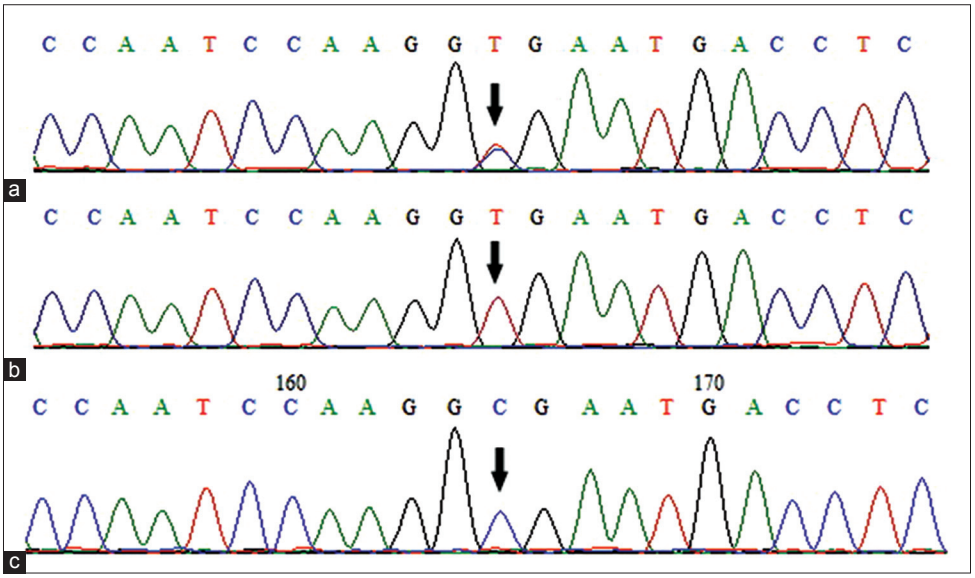

Figure 2: Genomic DNA sequencing (a) of the patient's mother, (b) the patient and (c) a normal individual

most common form of palmoplantar keratoderma in Japan and China and therefore, the mutation c. 796C>T was suggested to be screened preferentially in patients suspected to have this condition.[3]

To date, there are eight different mutations in *SERPINB7* reported, including four predicted to affect splicing sites (c.455-1G>A, c.455G>T, c.336 + 2T>G, and c.218_219delinsTAAACTTTACCT), two frameshift mutations (c.522-523insT and c.650_653del), one nonsense mutation (c.796C>T) and one missense mutation (c.830C>T).[2-5] No obvious genotype-phenotype correlation has been determined and no remarkable difference in clinical severity between patients harboring different mutations have been identified. Interestingly, skin lesions continued to progress even after puberty in our patient, in contrast to the typical non-progressive course after childhood in most patients. She also had much more widespread lesions involving the shins, lower thighs, distal forearms and perianal areas, as well as leukokeratosis and fissuring of her tongue which were not reported in

Table 1: The 51 palmoplantar keratoderma or ichthyosis-associated genes tested by our customized kit

Disorders	Inheritance pattern	Gene name
Ichthyosis	AR	*TGM1*, *SPINK5*, *CYP4F22*, *ABCA12*, *LIPN*, *CSTA*, *CLDN1*, *FLG*, *ALOXE3*, *NIPAL4*, *ERCC3*, *GTF2H5*, *ERCC2*, *SLC27A4*, *ALOX12B*, *PNPLA1*, *ABHD5*, *ALDH3A2*, *ELOVL4*, *ST14*, *SNAP29*, *SRD5A3*, *AP1S1*, *CSTA*
	AD	*KRT1*, *KRT2*, *KRT10*, *GJB2*, *GJA1*, *GJB3*, *GJB4*, *GJB6*
	X-linked	*NSDHL*, *STS*, *MBTPS2*
Palmoplantar keratoderma	AR	*CTSC*, *SLURP1*, *JUP*, *PKP1*, *POMP*
	AD	*KRT9*, *AAGAB*, *LOR*, *DSG1*, *DSP*, *KRT6A*, *KRT6B*, *KRT16*, *KRT17*, *COL14A1*, *TRPV3*

AR: Autosomal recessive, AD: Autosomal dominant

patients with Nagashima-type palmoplantar keratosis previously. Since no pathogenic mutations in other known causative genes for ichthyosis and palmoplantar keratoderma were detected in the proband, we reasoned that homozygous mutation c.796C>T in *SERPINB7* probably contributed greatly, if not fully, to this unusual phenotype. Furthermore, the mother, who is a heterozygous carrier of c.796C>T, showed mild non-progressive palmoplantar keratoderma since childhood. Since pseudodominant-inheritance pattern has been reported in a family with this condition, we sequenced all the coding and flanking sequences of *SERPINB7* in the mother but no additional mutations or variants were detected.[4] As the patient's brother, who was a heterozygous carrier for the mutation, was not affected, we inferred that added genetic deficiencies, for example, loss-of-function mutations in other serpin genes that are expressed in skin such as *SERPINB3*, *SERPINB4* or *SERPINB8*, may play an important role in the phenotypic expression and clinical severity of the disease in the family. Further studies are required to verify this hypothesis.

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Conflicts of interest

There are no conflicts of interest.

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