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Nagashima-type palmoplantar keratosis in Finland caused by a *SERPINB7* founder mutation

To the Editor: Nagashima-type palmoplantar keratosis (NPPK) is an autosomal recessive PPK caused by mutations in the serpin family B member 7 (*SERPINB7*) gene.[1] It has been reported only in Japanese, Chinese, and Korean populations, with a common founder mutation c.796C>T p.(Arg266*).[1-3] NPPK is characterized by well-demarcated, mild, nonprogressive, diffuse hyperkeratosis with transgradient erythema expanding onto the dorsal aspect of the hands, wrists, and Achilles tendon area. Palmoplantar hyperhidrosis, aquagenic whitening, and fungal infections are frequent.[1,4] Loss of functional SERPINB7 in skin probably leads to overactivation of intracorneocyte proteases causing skin barrier defects with hyperkeratosis, mild inflammation, and increased water permeability.[1]

We report 3 non-Asian patients with NPPK, with a typical NPPK phenotype and homozygous *SERPINB7* mutation. Since the age of 2 months, the 27-year-old Finnish male proband (P1) had a mild diffuse PPK with a well-demarcated erythema extending to the wrist and Achilles tendon area (Fig 1, Table I). His whole exome sequencing (Supplemental Text 1, available at Mendeley doi: 10.17632/z8tjpfdj3v.1) revealed a homozygous *SERPINB7* c.1136G>A p.(Cys379Tyr) (NM_003784.3) variant (rs201208667) in exon 8 encoding the second-last amino acid of *SERPINB7*. His unaffected mother and sister were heterozygous carriers of the variant.

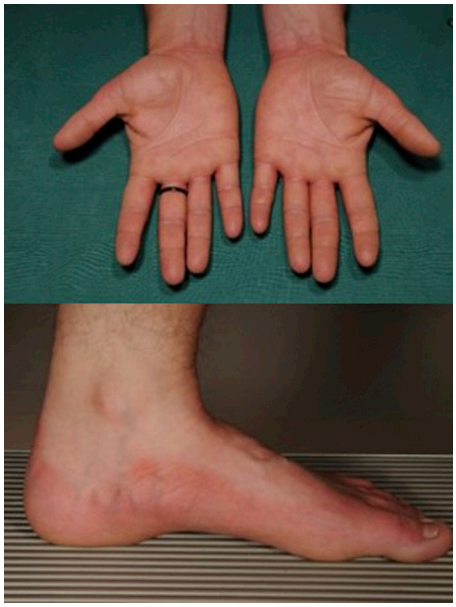

Fig 1. Clinical characteristics of Nagashima-type palmoplantar keratosis. Mild palmoplantar hyperkeratosis with transgradient erythema extending to the wrist and Achilles tendon area in P1 homozygous for *SERPINB7* c.1136G>A.

Sanger sequencing among 44 unrelated Finnish patients with PPK revealed 2 other homozygous patients and 4 heterozygous carriers (Table I). Whole exome sequencing of 3 heterozygous patients (P4, P5, and P6) revealed no other likely pathogenic variants or copy-number variations in *SERPINB7* or other genes. Whole exome sequencing was unfeasible for P7, but a single nucleotide polymorphism array for haplotype analysis revealed no other *SERPINB7* variants or copy-number variations. The cause of their PPK thus remains unknown. Other plausible *SERPINB7* variants were not analyzed in the other patients.

SERPINB7 c.1136G>A p.(Cys379Tyr) has not been reported in NPPK (Supplemental Table 1, available at Mendeley doi: 10.17632/z8tjpfdj3v.1). It was predicted damaging by Sorting Intolerant From Tolerant (SIFT), Polymorphism Phenotyping (PolyPhen), MutationTaster, logistic regression test (LRT), and Combined Annotation Dependent Depletion (CADD) (score 19). Only heterozygous

Table I. Clinical characteristics of the patients

Variable	P1	P2	P3	P4	P5	P6	P7	P1 mother	P1 sister	NPPK
SERPINB7 c.1136G>A (rs201208667)	A/A	A/A	A/A	G/A	G/A	G/A	G/A	G/A	G/A	–
Whole exome sequencing*	+	–	–	+	+	+	–	–	–	
Age, y	27	18	11	60	21	12	16	66	32	
Sex	Male	Male	Male	Male	Female	Female	Male	Female	Female	
Age of onset	2 mo	Birth	1.5 y	Early childhood	Early childhood	Birth	9 y	–	–	Birth to 9-10 y
Diffuse mild PPK	+	+	+	+	+	+	+	–	–	+
Transgradients	+	+	+	+	+	+	+	–	–	+
Achilles tendon affected	+	+	+	–	+	+	–	–	–	+
Wrists affected	+	+	+	–	+	+	–	–	–	+
Progrediens	–	–	–	–	–	–	–	–	–	–
Hyperhidrosis	+	+	+	+	+	+	+	–	–	+/–
Aquagenic whitening	+	+	+	N/A	+	+	–	–	–	+
Fungal infections	+	–	–	–	+	+	+	–	–	+
Knee/elbow hyperkeratosis	–	–	–	–	–	–	–	–	–	+/–

+, Present; –, not present; *N/A*, not applicable; *NPPK*, Nagashima-type palmoplantar keratosis; *P*, patient; *PPK*, palmoplantar keratosis.
*Whole exome sequencing: +, done; –, not done.

carriers were found in population allele frequency databases (Exome Aggregation Consortium [ExAC], Genome Aggregation Database [GnomAD], and Sequencing Initiative Suomi [SISu]). According to GnomAD, the heterozygous carrier frequency was significantly higher for the Finnish population (0.006397) than for non-Finns (0.00032-0.0014), indicating a 5- to 20-fold enrichment in Finns. A common haplotype spanning 272 kilobase (kb) around the detected variant was shared by P1, P2, and 6 heterozygous carriers, according to genome-wide single nucleotide polymorphism array data (Supplemental Table 2, available at Mendeley doi: 10.17632/z8tjpfdj3v.1). The variant thus constitutes a plausible Finnish NPPK founder mutation.

The skin histology of P1 showed nonepidermolytic hyperkeratosis compatible with NPPK. SERPINB7 immunostaining was strong throughout the stratum spinosum, with the most intense staining in the stratum granulosum. Heterozygous carriers and healthy controls showed less intense staining throughout the stratum spinosum and the lower stratum spinosum was negative (Supplemental Fig 1, available at Mendeley doi: 10.17632/z8tjpfdj3v.1). Thus, the c.1136G>A p.(Cys379Tyr) mutation apparently leads to aberrant SERPINB7 distribution within the stratum spinosum.

The c.1136G>A p.(Cys379Tyr) *SERPINB7* variant changes the second-last amino acid cysteine, which is conserved among different species (Supplemental Fig 2, available at Mendeley doi: 10.17632/z8tjpfdj3v.1). Tertiary structure prediction suggested that the substitution is in the vicinity of the reactive site loop where most *SERPINB7* mutations in NPPK are located. The substitution possibly affects the conformational mobility of the reactive site loop during the inhibition process.[5]

Previously NPPK has been reported exclusively in Asian patients. Our findings encourage assessment for *SERPINB7* mutations in non-Asian individuals with an NPPK-phenotype.

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Evaluation of the psychosocial impact of a Social Interaction Skills Training (SIST) workshop for patients with vitiligo: A pilot study

To the Editor: Vitiligo may significantly impair quality of life, particularly in social functioning and interpersonal interactions.[1] Psychosocial interventions remain scarce, however. Social Interaction Skills Training (SIST) has been shown to significantly reduce social anxiety and avoidance and improve confidence in patients with visible differences.[2] SIST incorporates cognitive behavioral therapy principles, using coping mechanisms to retrain maladaptive thinking patterns and communication techniques to reframe interactions. Common techniques include social dynamic exploration, behavioral modeling, role playing, feedback, and coaching.

We developed a SIST workshop for vitiligo patients (Supplemental Table I, available at https://doi.org/10.17632/rcw37kjcrp.1), based on principles emphasized by Robinson et al and the British charity Changing Faces.[2] Primary end points included the Social Avoidance and Distress (SAD) Scale.[3] Secondary end points included the Brief Fear of Negative Evaluation-II (BFNE-II) Scale,[3,4] 2 visual analog scales[5] assessing comfort levels in social situations, and open-ended workshop-specific questionnaires. The SAD, BFNE-II, and visual analog scales are standardized instruments validated in measuring social avoidance and anxiety.

This prospective pilot study, which was approved by the University of Texas Southwestern Medical Center Institutional Review Board, recruited 17 patients with vitiligo from the University of Texas Southwestern Medical Center Pigmentary Disorders Clinic (Table I). All were 18 years or older, fluent in English, had no significant neuropsychiatric history, and attended one of two 6-hour SIST workshops facilitated by clinical psychologists. Participants completed the outcome measures at 4 separate times: immediately before and after the workshop and again 3 and 8 weeks afterwards.

A repeated-measures analyses of variance was performed to assess quantitative scores (Table II), using imputation with the last-observation-carried-forward method to address any missing data. An inductive thematic analysis was conducted to