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

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

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Capsule summary

- *SERPINB7* mutations in NPPK are not confined to Asian populations.
- The presence of *SERPINB7* mutations should be tested in patients with NPPK in non-Asian populations.

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*).[1,2,3] NPPK is characterized by well-demarcated, mild, nonprogressive diffuse hyperkeratosis with transgredient 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 three non-Asian NPPK patients, with a typical NPPK phenotype and homozygous *SERPINB7* mutation. Since the age of two 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 (WES) (SuppText1) 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. Sanger sequencing among 44 unrelated Finnish PPK patients revealed two other homozygous patients and four heterozygous carriers (Table I). WES of three heterozygous patients (P4-P6) revealed no other likely pathogenic variants or copy-number variations (CNVs) in *SERPINB7* or other genes. WES was unfeasible for P7 but a SNP array for haplotype analysis revealed no other *SERPINB7* variants or CNVs. 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 (SuppTable1). It was predicted damaging by SIFT, Polyphen, MutationTaster, LRT and CADD (score 19). Only heterozygous carriers were found in population allele frequency databases (ExAC, GnomAD and SISu). According to GnomAD, the heterozyogous 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 kb around the detected variant was shared by P1, P2 and six heterozygous carriers, according to

genome wide SNP array data (SuppTable2). The variant thus constitutes a plausible Finnish NPPK founder mutation.

P1's skin histology showed non-epidermolytic hyperkeratosis compatible with NPPK. SERPINB7 immunostaining was strong throughout the stratum spinosum (SS) with most intense staining in stratum granulosum. Heterozygous carriers and healthy controls showed less intense staining throughout the SS and the lower SS was negative (SuppFigure 1). Thus, the c.1136G>A p.(Cys379Tyr) mutation apparently leads to aberrant SERPINB7 distribution within the SS.

The c.1136G>A p.(Cys379Tyr) *SERPINB7* variant changes the second-last amino acid cysteine, which is conserved among different species (SuppFigure2). Tertiary structure prediction suggested that the substitution is in the vicinity of the reactive site loop (RSL) where most *SERPINB7* mutations in NPPK are located. The substitution possibly affects the conformational mobility of RSL 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 a NPPK-phenotype.

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Abbreviations

NPPK: Nagashima type palmoplantar keratoderma

PPK: palmoplantar keratoderma

SERPINB7: serpin family B member 7

WES: Whole exome sequencing

CNV: copy-number variation

RSL: reactive site loop

SiSU: Sequencing Initiative Suomi project

SS: stratum spinosum

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Figure legends

Figure 1. NPPK clinical characteristics**.** Mild palmoplantar hyperkeratosis with transgredient erythema extending to the wrist and Achilles tendon area in P1 homozygous for *SERPINB7* c.1136G>A.

Table legends

Table I. Clinical characteristics of the patients.

Supplemental material on Mendeley platform

SuppTable1. *SERPINB7* mutations in NPPK. Founder mutations are highlighted in bold.

SuppTable2. Shared haplotype around *SERPINB7* c.1136G>A p.(Cys379Tyr) variant (rs201208667). Two homozygous patients and six heterozygous carriers show the common shared 272 kb haplotype delineated by the black lines. Shared haplotype regions are shaded light grey and the c.1136G>A p.(Cys379Tyr) variant is bolded and shaded dark grey. The haplotypes of P1, P1's mother and sister and P2 extend beyond the region shown.

SuppText1. Materials and methods.

SuppFigure1. NPPK clinical characteristics and SERPINB7 immunohistochemistry**.**

SuppFigure2. Conservation of Cys379 among different species and in SERPIN family members.

143 **Tables**

144 Table I. Clinical characteristics of the patients.

	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	-
WES*	+	-	-	+	+	+	-	-	-	
Age years	27	18	11	60	21	12	16	66	32	
Gender	male	male	male	male	female	female	male	female	female	
Age of onset	2 months	birth	1.5 years	Early childhood	Early childhood	birth	9 years	-	-	birth to 9-10 years
Diffuse mild PPK	+	+	+	+	+	+	+	-	-	+
Transgredient	+	+	+	+	+	+	+	-	-	+
Achilles tendon affected	+	+	+	-	+	+	-	-	-	+
Wrists affected	+	+	+	-	+	+	-	-	-	+
Progrediens	-	-	-	-	-	-	-	-	-	-
Hyperhidrosis	+	+	+	+	+	+	+	-	-	+ /-
Aquagenic whitening	+	+	+	N/A	+	+	-	-	-	+
Fungal infections	+	-	-	-	+	+	+	-	-	+
Knee/elbow hyperkeratosis	-	-	-	-	-	-	-	-	-	+ /-

145 *WES, whole exome sequencing done +/ not done

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