SPANDIDOS PUBLICATIONS

MOLECULAR MEDICINE REPORTS 14: 4049-4054, 2016

Nagashima-type palmoplantar keratosis in a Chinese Han population

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Received July 11, 2015; Accepted May 13, 2016

DOI: 10.3892/mmr.2016.5757

Abstract. Nagashima-type palmoplantar keratosis (NPPK) is an autosomal recessive form of palmoplantar keratoderma (PPK), which is caused by mutations in the *SERPINB7* gene. NPPK has only been reported in Japanese and Chinese populations. The present study was conducted on 12 unrelated Chinese patients who were clinically predicted to suffer from NPPK. Mutation screening was performed by direct sequencing of the entire coding regions of *SERPINB7*, *SLURP1*, *AQP5*, *CSTA*, *KRT1* and *KRT9* genes. Direct sequencing of *SERPINB7* revealed five homozygous founder mutations (c.796C>T) and four compound heterozygous mutations in nine patients, including one novel mutation (c.122_127delTGGTCC). Nine out of the 12 patients were diagnosed with NPPK due to *SERPINB7* pathogenic mutations, and the results expanded the known mutation spectrum of NPPK. Taking the other seven reported Chinese patients, who had been definitively diagnosed with NPPK by genetic testing, into account, the present study further demonstrated that NPPK is a common entity in Mainland China, and c.796C>T is the most prevalent mutation and exerts a founder effect. Furthermore, the NPPK cases described in the current study presented a consistently mild phenotype, as compared with the degrees of phenotypic variability associated with other types of relatively severe PPK, including Mal de Meleda and Olmsted syndrome.

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Key words: Nagashima-type palmoplantar keratosis, SERPINB7, Chinese

Introduction

Nagashima-type palmoplantar keratosis (NPPK; OMIM #615598) is an autosomal recessive form of palmoplantar keratoderma (PPK), which exhibits a relatively high incidence and has only been reported in Japanese and Chinese populations (1,2). The characteristic features of NPPK are erythema and hyperkeratosis of the palms and soles, with sharp demarcation that mainly extends to the wrists, ankles, Achilles tendon area, and the dorsal aspects of the fingers and toes (1). Furthermore, other frictional regions, such as knees and elbows, may be involved. Some patients with NPPK also exhibit associated palmoplantar features, including a white, spongy appearance within 10 min of water exposure, hyperhidrosis and fungal infections (3).

The clinical features of diffuse PPK and the recessive mode of inheritance are not unique characteristics for NPPK, but are also associated with autosomal recessive exfoliative ichthyosis (AREI; OMIM #607936), which is caused by mutations in cystatin A (*CSTA*) (4), and an atypical mild form of Mal de Meleda (MDM; OMIM #248300), which is caused by mutations in secreted LY6/PLAUR domain containing 1 (*SLURP1*) (5). Other types of autosomal dominant diffuse PPK with *de novo* mutations include Unna-Thost type PPK [OMIM #600962; corresponding gene, keratin (*KRT*)*1*], Vorner type PPK (OMIM #144200; corresponding gene, *KRT9*/*KRT1*) and Bothnian type PPK [OMIM 600231; corresponding gene, aquaporin 5 (*AQP5*)], which must be differentiated from NPPK (3).

Mutations in the serpin peptidase inhibitor, clade B (ovalbumin), member 70 (*SERPINB7*) gene, which encodes a member of the serine protease inhibitor superfamily, results in a complete loss of protease inhibitory activity. *SERPINB7* mutations were reported to be responsible for NPPK in 2013 (3).

At present, only 31 unrelated, molecularly diagnosed cases of NPPK associated with seven distinct pathogenic *SERPINB7* mutations in the homozygous or compound heterozygous state have been reported in the literature. These cases include the most popular founder mutation c.796C>T, and other potentially frequent mutations c.218_219del2ins12, c.336+2T>G, c.455-1G>A, c.455G>T, c.522dupT and c.650_653delCTGT (2,3,6,7). Among these studies, only one report regarding

seven cases of NPPK associated with four different *SERPINB7* mutations was available in Mainland China (2).

The present study investigated 12 suspected Chinese patients with NPPK. Nine of the participants were definitely diagnosed with NPPK by molecular analysis.

Materials and methods

Subjects. The present study was approved by the Institutional Review Board of Xinhua Hospital, Shanghai Jiaotong University School of Medicine (Shanghai, China). All participants provided written informed consent. Patients suspected as having NPPK were recruited by experienced dermatologists from Xinhua Hospital and Shanghai Skin Hospital (Shanghai, China). In total, 12 probands (8 females and 4 males), nearly all of their parents (except for the parents of Patients 11 and 12, and the father of Patient 10), and 100 population-matched healthy controls were enrolled in the present study between August 2006 and December 2014. All probands were genetically unrelated ethnic Han Chinese, which exhibited non-progressive, symmetrical, diffuse erythema and hyperkeratosis over the palms and soles from infancy. Elbow and knee involvement was not observed. The clinical appearance of three patients (Patients 1, 3 and 10; 8 months old, 19 years old and 22 years old, respectively) is presented in Figs. 1-3. Clinical details were available for 10 of the 12 patients. The age group ranged between 8 months and 51 years. The age of onset was ~3 months (Table I). No family history and consanguinity was identified in this cohort.

Methods. Peripheral blood samples were collected from all participants for DNA extraction. DNA was extracted using a TIANamp Blood DNA kit (Tiangen Biotech Co., Ltd., Beijing, China) and PCR primers were designed flanking all coding exons and intron-exon boundaries of six genes (*SERPINB7*, *SLURP1*, *AQP5*, *CSTA*, *KRT1* and *KRT9*) using Primer Premier 5.0 software (Premier Biosoft, Palo Alto, CA, USA; Table II). Genomic DNA samples were amplified by standard polymerase chain reaction and the PCR protocol was as follows: i) Denaturation, 94˚C for 5 min; ii) 31 cycles of denaturation at 94˚C for 30 sec, annealing for 30 sec at temperatures according to the primers for each fragment, and extension at 72˚C for 1 min; iii) extension, 72˚C for 1 min; and iv) extension, 4˚C for 5 min. PCR was repeated 10-20 times. Sanger sequencing was performed using an ABI PRISM®3730 automated sequencer (Applied Biosystems; Thermo Fisher Scientific, Inc., Waltham, MA, USA). The *SERPINB7* gene, which is associated with autosomal recessive NPPK, was tested initially. If no corresponding mutations in two alleles were identified, the other five genes were sequentially sequenced. Identified mutations were respectively confirmed in the unaffected family members (if available) and 100 population-matched healthy controls (if mutation is novel).

Results

Mutations identified in *SERPINB7* (GenBank accession number: NM_001040147.2) are summarized in Table I. The present study detected five homozygous founder mutations (c.796C>T) and four compound heterozygous mutations (c.796C>T combined with c.455G>T, c.522dupT or c.122_127delTGGTCC) in nine patients with NPPK (Fig. 4). Among the mutations, the in-frame deletion mutation c.122_127delTGGTCC has not previously been reported, and was also absent in the 100 population-matched healthy controls. Furthermore, indexed unaffected parents in the present cohort were all heterozygous carriers. Notably, the other three patients were revealed to harbor one heterozygous founder mutation (c.796C>T) in *SERPINB7*, whereas no pathogenic mutations were detected in the five remaining candidate genes.

Discussion

All of the seven previously reported pathogenic mutations associated with NPPK (c.218_219del2ins12, c.336+2T>G, c.455-1G>A, c.455G>T, c.522dupT, c.650_653delCTGT, c.796C>T) are nonsense/frameshift/splice site mutations, which form premature stop codons and truncate the protein, thus suggesting that missense variants without splicing effects tend to be non-pathogenic polymorphisms. The novel mutation c.122_127delTGGTCC (p.Leu41_Val42del) identified in the present cohort was estimated to cause an in-frame deletion of two amino acid residues (leucine and valine). Considering patient 10 exhibited the typical features of NPPK (Fig. 3), and the in-frame deletion mutation was not detected in 200 alleles from the 100 healthy controls, it was predicted that this mutation may shorten the protein, and exert pathogenic effects resulting in an NPPK phenotype.

Notably, three suspected patients with typical palmoplantar lesions of NPPK were all shown to harbor one heterozygous founder mutation (c.796C>T) in *SERPINB7*, whereas no pathogenic mutations were identified in the remaining five candidate genes responsible for analogous genodermatoses. It has previously been reported that female carriers with missense *SLURP1* mutations may exhibit mild palmar lesions (8), whereas a heterozygous *SERPINB7* mutation did not induce any palmoplantar abnormalities, thus indicating that either of the alleles can retain protein activity of SERPINB7 and sustain normal skin structure. Therefore, the three suspected cases very probably suffer from NPPK. In addition, novel mutations in the other allele may be undetectable large deletions, or mutations located in other loci of *SERPINB7*, including deep introns and 5'/3'-untranslated regions, which require more intensive investigations, such as RNA testing or next-generation sequencing. Unfortunately, these samples are not available for retesting.

The major etiological factor associated with MDM is consanguineous marriage (9,10), and MDM has been diagnosed in the Mediterranean region, the Middle East, Europe and East Asia. Conversely, NPPK appears to be an Asian-only endemic (11), the prevalence rate of which has been estimated to be 1.2/10,000 and 3.1/10,000 in Japanese and Chinese Han populations, respectively (3). Furthermore, the most common mutation (c.796C>T) exerts a founder effect and contributes to NPPK etiology (2).

In order to detect other *SERPINB7* variants with a worldwide range that harbor the potential for being pathogenic, they were searched for using the 1000 Genomes Browser Version 3.0.2 (http://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/).

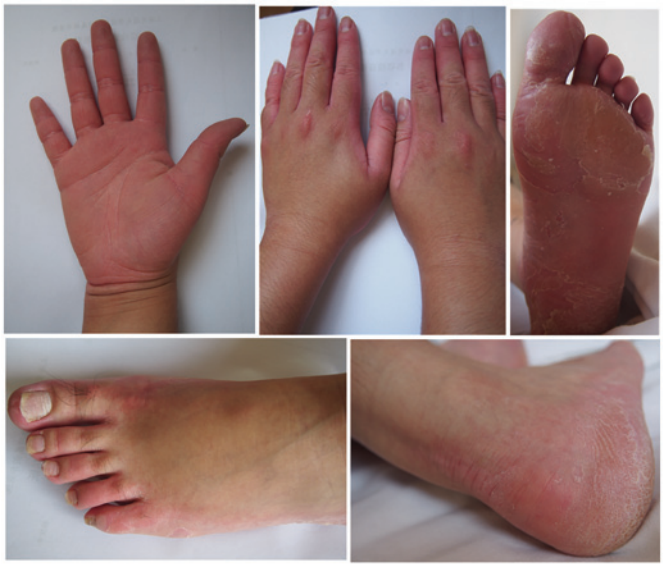

Figure 1. Clinical appearance of a 19-year-old patient with a homozygous c.796C>T mutation.

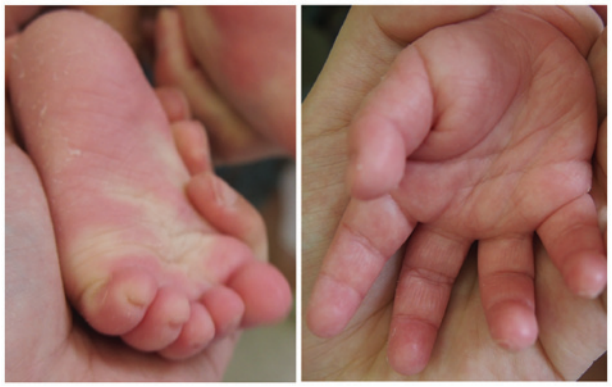

Figure 2. Clinical appearance of an 8-month-old patient with a homozygous c.796C>T mutation.

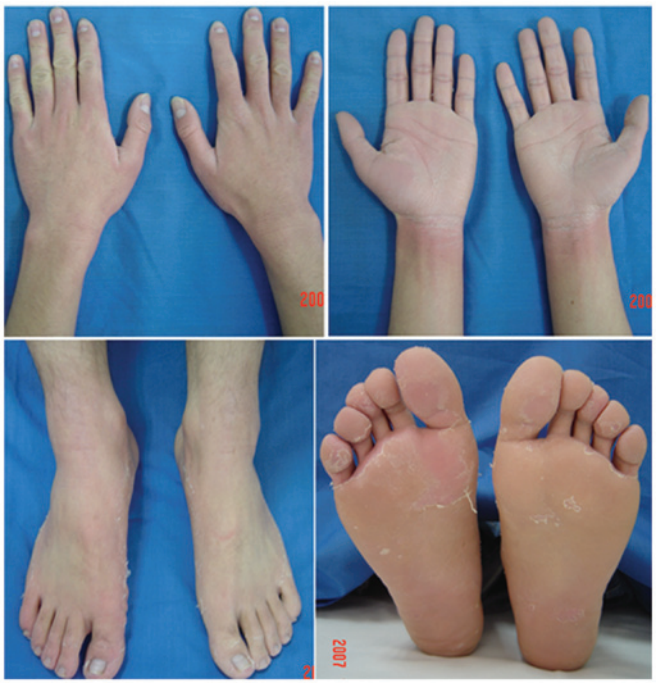

Figure 3. Clinical appearance of a 22-year-old patient with a novel c.122_127delTGGTCC mutation.

The corresponding results are summarized in Table III. Furthermore, in combination with previous studies, the c.218_219del2ins12 mutation has only been detected in the Japanese population; the c.522dupT and c.650_653delCTGT mutations were only detected in the Chinese Han population; and four known pathogenic mutations (c.336+2T>G, c.455-1G>A, c.455G>T and c.796C>T) existed in both populations (2,3,7). Notably, c.455G>T and c.522dupT have been reported in two unrelated patients, and the c.455G>T mutation has a high allele frequency of 0.0025, in the Chinese Han population, thus suggesting a potential founder effect (7).

SERPINB7 is expressed in the epidermis of the whole body, and belongs to a cluster of clade-B serpins that inhibit serine proteases and protect cells from exogenous and endogenous proteolysis (12). Notably, absence of the critical reactive site loop (P17-P50; amino acid residues, 331-352) is predicted to be responsible for skin abnormalities in NPPK. All of the identified mutations, with the exception of the novel mutation detected in the present cohort, are expected to truncate the reactive site loop, thus resulting in NPPK phenotypes. The precise function of SERPINB7 remains poorly defined. Sakabe *et al* (13) speculated that the pathogenesis of NPPK may be associated with the effects of T cells infiltrating into the skin, thus suggesting a potential treatment with topical drugs that inhibit T cell infiltration, such as tacrolimus ointment.

The causal genes of PPK are associated with variable phenotypes (5). *SLURP1* mutations may cause mild MDM without plantar, nail, knee and elbow involvement, as well as severe complications, including higher occurrence of malignant melanoma in the hyperkeratotic area (14). *TRPV3* mutations result in Olmsted syndrome (OMIM #614594) with bilateral mutilating palmoplantar hyperkeratosis and periorificial keratotic plaques, along with focal PPK with mild acropodium deformation (15). *SERPINB7*-associated NPPK has been reported to exhibit little phenotypic heterogeneity, corresponding hyperkeratotic lesions with a reddish appearance that predominantly occur in chronic mechanical stress-exposed areas of the skin, and a non-progressive disease course (3), all of which were also observed in the present cohort (Figs. 1-3). These clinical phenomena suggested that except for the distinct pathogenic mechanisms of corresponding genes, external stimuli, such as injury and friction, may also be crucial factors associated with the occurrence of NPPK phenotypes, which is similar to the findings of our previous report regarding the progression of MDM (16). Furthermore, taking into account other potential factors, including epigenetic alterations, modifier genes and ethnic background, sometimes diseases with a diffuse PPK appearance are analogous and hard to differentiate. For instance, the clinical photographs in previously published studies regarding clinically suspected NPPK seem to bear close similarity to mild or early stage MDM due to the yellowish palmoplantar lesions (5,17), which differ from the usual

Table I. Identified *SERPINB7* mutations in the present cohort.

			Molecular results			
			Allele 1		Allele 2	
Patient no.	Gender/ age	Age at first symptom	Nucleotide change	Amino acid change	Nucleotide change	Amino acid change
1	M/8 m	2 m	c.796C>T	p.R266*	c.796C>T	p.R266*
2	F/2 y	1 w	c.796C>T	p.R266*	c.522dupT	p.Val175fs
3	F/19 y	3 m	c.796C>T	p.R266*	c.796C>T	p.R266*
4	M/4 y	6 m	c.796C>T	p.R266*	c.796C>T	p.R266*
5	M/16 y	3 m	c.796C>T	p.R266*	?	?
6	F/26 y	2 m	c.796C>T	p.R266*	c.796C>T	p.R266*
7	F/17 y	2 m	c.796C>T	p.R266*	?	?
8	F/24 y	5 m	c.796C>T	p.R266*	?	?
9	F/36 y	?	c.796C>T	p.R266*	c.796C>T	p.R266*
10	M/22 y	3 m	c.796C>T	p.R266*	c.122_127delTGGTCC	p.Leu41fs
11	F/51 y	?	c.796C>T	p.R266*	c.522dupT	p.Val175fs
12	F/2 y	2 m	c.796C>T	p.R266*	c.455G>T	Predicted splicing alteration

SERPINB7, serpin peptidase inhibitor, clade B (ovalbumin), member 70; M, male; F, female; w, weeks; m, months; y, years; ?, unknown.

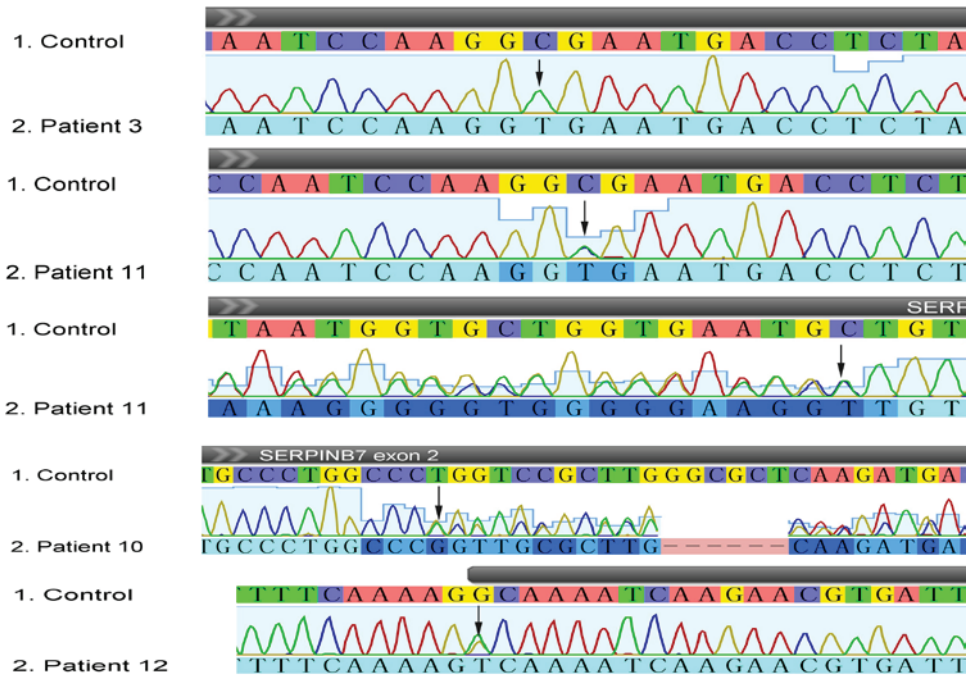

Figure 4. Sequencing results of representative serpin peptidase inhibitor, clade B (ovalbumin), member 70 (*SERPINB7*) mutations in the present study. From top to bottom, the sequencing results are c.796C>T (homozygous) in Patient 3, c.796C>T along with c.522dupT (heterozygous) in Patient 11; c.796C>T along with c.122_127delTGGTCC (heterozygous) in Patient 10; and c.796C>T along with c.455G>T (heterozygous) in Patient 12. Arrows indicate the site of mutation.

reddish appearance in pediatric patients with NPPK (Fig. 2). In addition, other diseases, such as AREI, Unna-Thost type PPK and Bothnia type PPK, are difficult to clinically distinguish, which further underlines the complexity of clinical differential diagnoses between diseases with palmoplantar hyperkeratosis and without other associated features, as well as the importance of molecular analysis.

In conclusion, the present report focused on patients in Mainland China, with respect to nine definite and three suspected patients with NPPK. The results revealed three recurrent and one novel *SERPINB7* mutation, thus extending the mutation spectrum of NPPK. Taking the other seven reported Chinese patients, that were definitively diagnosed with NPPK by genetic testing, into account, the present

Table II. Primers of the six screening genes (*SERPINB7*, *SLURP1*, *CSTA*, *AQP5*, *KRT1* and *KRT9*).

Primer name	Primer sequence		Primer size (bp)
	Forward	Reverse	
SERPINB7-E02	CAGAAATGTCCACCAACGAG	ATATTTCTGCTGCCTCTTGG	608
SERPINB7-E03	CTTTCCTTGTGCCCTGTTTA	TTAAGCTAACCTCCCACCAT	295
SERPINB7-E04	GGGCAAGAAAGGATGAAGTT	CATCCCTACCAATAGACACG	704
SERPINB7-E05	CCTTCCAGTCCCATTTCCAT	GAGGGTGAGATATTGAGGTT	615
SERPINB7-E06	CACAGGGATTATGTAAGGAT	ACACGTTTGGTGGTGTTTCA	559
SERPINB7-E07	ACCCAAGGTCACATAGTTAG	CTAGTATCTCAATACCCTGA	485
SERPINB7-E08	TCACCTGTCTATTGCTCCAC	ATTGACTTGTGGTGGTTCTT	765
SLUPR1-E01	CAGAGGCACAGCCAGGACAT	TAGGAGGTGGGCAGACAAGC	470
SLUPR1-E02	TCTGTGGCTCAGCTCAGTTAGA	TCCCTGTTCCCAATAGTCCA	709
SLUPR1-E03	TGGACTATTGGGAACAGGGATC	GGTTCAGAGTTCCGAGTTGC	257
CSTA-E01	TAAAACACGAGTCTCCACACT	AAAGCCACAAACATCCTAAA	256
CSTA-E02	ACTTTTAGGAGGATGAGGTT	AAGGAATTATGTGGTAGGGA	284
CSTA-E03_NEW	ACCCATTTGAATGAATCTCC	CCAGTTGCATTAGGCTTGAC	433
AQP5-E01	CGCCGCATCCACCTCCTCCG	CCCCAGGGTCGAGGCTCCCA	486
AQP5-E02	AAAAGCCCTACTCCCCGAGC	GATTCCTGTCCCATCCCACC	466
AQP5-E03	CAGGAATCAAACCCAACCTC	TCCCTTTCTCTGTCAGCCAC	442
AQP5-E04	CGCTCTGTTCATCCGTCTCT	TTTCTTCTTTTCCCCCTTGG	576
KRT1-E01A	CCAAGCCCAATTTCTTCCCTG	AAGGCTCTGGTTGATAGTGA	549
KRT1-E01B	TGGAAGTCGGAGTCTTGTTA	ATTCAACAGATATGAGTCCC	696
KRT1-E02	GTATGCGCTTTGCTATTGGT	ATTGCCTATCACTGCCTTTC	684
KRT1-E03	TTAGGTTAGAGGCACATCAG	AAATGTGAGTTCCGTCCTAC	313
KRT1-E04+05	CCATATTTCCCAGCACCTTA	AGATGGTAGATAGCGTTTGT	794
KRT1-E06	CAAGGTGAGTGGGCTGAAAG	CTCACATTGACCATCCCATC	492
KRT1-E07	AGTCTGTAAGGGTTGTAGGAG	GAATAATTTGCTCCACCTCA	699
KRT1-E08+09	GCGGTTTGGGAAGCTGGAGT	TTGAAATGTCATGTGGGTGG	877
KRT9-E01_in	CGGTAGCACTCCTATCACTGC	CTGCTCTGCCCAAACTCTGAA	931
KRT9-E02+03	ATCTTCGCTGAAGGCTGGAA	AAGCCAAAGCCCAACCACTA	701
KRT9-E04	GTGGTTGGGCTTTGGCTTCA	GGAGGTGGGAGGGATGGAGA	356
KRT9-E05+06	GACTTGTCATTGGCTTCAGA	CAGAGGGACAGAAGTAGTATCA	664
KRT9-E07	AGATTCATGTTTGGGTCCTG	CCCTTACCTTTTGTCTCATCT	621

Table III. Allele frequencies of known pathogenic mutations (in bold) and other potential pathogenic variants in distinct population.

Mutation	Nucleotide change	Amino acid change	Allele frequencies in distinct populations					
			Han	Japanese	African	American	European	All
rs201433665	**c.336+2T>G**	p.?	0.0025	0	0	0	0	<0.001
rs202182550	**c.455G>T**	p.?	0.0025	0	0	0	0	<0.001
rs142859678	**c.796C>T**	p.Arg266*	0.017	0.014	0	0	0	0.002
rs182539714	c.-16T>A	p.?	0.005	0.005	0	0	0	0.001
rs199666937	c.140A>G	p.Gln47Arg	0	0	0	0	0.001	<0.001
rs74653657	c.181A>G	p.Asn61Asp	0.012	0	0	0	0	0.002
rs201239910	c.388G>A	p.Asp130Asn	0	0	0.001	0	0	<0.001
rs201821537	c.219+8C>A	p.?	0	0	0	0.001	0	<0.001
rs186928560	c.220-6T>G	p.?	0	0	0	0	0.001	<0.001
rs139542928	c.943C>T	p.Arg315Cys	0	0	0.001	0	0	<0.001
rs201208667	c.1136G>A	p.Cys379Tyr	0	0	0	0	0.001	<0.001

?, unknown.

study further demonstrated that NPPK is a common entity in Mainland China, and c.796C>T is the most prevalent mutation and exerts a founder effect. At present, there is no effective drug treatment for the majority of diffuse and severe forms of PPK, whereas the symptoms of NPPK are relatively milder and long-time prognosis is favorable. Considering the high allele frequency of the founder mutation, genetic counseling is essential for patients with NPPK or carriers of NPPK.

Acknowledgements

The present study was supported by grants from the Industry Foundation of Ministry of Health of China (grant no. 20120213), the Ph.D. Programs Foundation of Ministry of Education of China (grant no. 20130073120014), the Natural Science Foundation of Shanghai Jiaotong University School of Medicine (grant no. 13XJ10023) and a grant from the Foundation of Xinhua Hospital affiliated to Shanghai Jiaotong University School of Medicine (grant no. 15YJ15).

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