

## SHORT COMMUNICATION

Genetic Analysis of *CARD14* in Non-familial Pityriasis Rubra Pilaris: A Case SeriesJin-Bon Hong<sup>1,2</sup>, Pei-Lung Chen<sup>2,3</sup>, You-Tzung Chen<sup>2</sup> and Tsen-Fang Tsai<sup>1\*</sup><sup>1</sup>Department of Dermatology, <sup>2</sup>Graduate Institute of Medical Genomics and Proteomics, National Taiwan University Hospital and College of Medicine, NO. 7, Chun-Shan South Road, Taipei 100, and <sup>3</sup>Department of Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan. \*E-mail: tftsai@yahoo.com  
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Pityriasis rubra pilaris (PRP) is a papulosquamous disorder of unknown aetiology with distinctive but overlapping clinicopathological features with psoriasis. Recently *CARD14* mutations have been found in some familial cases of both diseases (1, 2). *CARD14* encodes a 1,004 amino acid protein, caspase recruitment domain-coding protein 14, which is an activator of NF- $\kappa$ B. Since most RPR patients are sporadic, it is worth screening for *CARD14* in non-familial PRP. Here, we report a *CARD14* gene analysis in 8 unrelated cases of typical sporadic PRP.

## CASE REPORTS

Cases were collected from 8 consecutive Taiwanese patients with PRP currently seen in our clinic. All individuals were diagnosed with PRP by typical clinical features with histological confirmation from skin biopsies. Genomic DNA was extracted from blood using the Chemagic DNA Blood Kit. The *CARD14* gene consists of 23 exons and spans 39340 bp. PCR was used to amplify the coding exons and flanking introns of the *CARD14* gene (RefSeq NM\_024110.4). Standard DNA sequencing reactions were performed using fluorescence-labelled dideoxy chain terminations with the Big Dye Terminator ABI Prism Kit and the ABI PRISM 3130xl DNA Analyzer (Applied Biosystems, Foster City, California).

Our case series of PRP included 6 male and 2 female Taiwanese patients without a family history. Clinical characteristics and genetic polymorphisms of the patients are summarised in Table I. One male patient had type III classic juvenile PRP with a unique history of recurrence in adulthood. One male patient had type IV circumscribed juvenile PRP. The other patients had type I adult generalised PRP.

The genomic sequence analysis on *CARD14* in the 8 sporadic PRP patients only revealed multiple single nucleotide polymorphisms (SNPs). The missense variants and the polymorphism at the splice junction are shown in Tables I and II. The missense variants were c.1641G>C (p.Arg547Ser), c.2458C>T (p.Arg820Trp), and c.2648G>A (p.Arg883His). All 8 patients had the polymorphism c.2399-4A>G at the splice junction. One female with severe type I PRP only had this polymorphism of splice junction without other missense variants. Seven patients had the missense variant c.2458C>T (p.Arg820Trp) and 5 patients had the missense variant

Table I. Clinical features and *CARD14* polymorphisms of patients with non-familial pityriasis rubra pilaris

Case/Sex	Onset (y/o)	Type	Skin manifestation	<i>CARD14</i> SNP
1/M	7	III	Diffuse	c.1641G>C (p.Arg547Ser) c.2399-4A>G
2/M	12	IV	Localised	c.2458C>T (p.Arg820Trp) c.1641G>C (p.Arg547Ser) c.2399-4A>G
3/M	20	I	Diffuse	c.2458C>T (p.Arg820Trp) c.1641G>C (p.Arg547Ser) c.2399-4A>G
4/F	24	I	Diffuse	c.2458C>T (p.Arg820Trp) c.2399-4A>G
5/F	34	I	Localised	c.2399-4A>G
6/M	39	I	Diffuse	c.2458C>T (p.Arg820Trp) c.1641G>C (p.Arg547Ser) c.2399-4A>G
7/M	51	I	Diffuse	c.2458C>T (p.Arg820Trp) c.2648G>A (p.Arg883His) c.2399-4A>G
8/M	60	I	Localised	c.2458C>T (p.Arg820Trp) c.1641G>C (p.Arg547Ser) c.2399-4A>G c.2458C>T (p.Arg820Trp)

c.1641G>C (p.Arg547Ser). These SNPs are common in the Asian population according to phase I 1000 Genomes Project database, which included 97 Han Chinese (Table II). The polymorphism c.2399-4A>G at the splice junction is not known to cause mRNA splice variant. The amino acid changes of missense polymorphisms are mapped to the GUK domain or other regions of the *CARD14* protein. To determine whether these non-synonymous SNPs affect the function of the *CARD14* protein and contribute to disease, Polymorphism Phenotyping version 2 (PolyPhen-2) software was used to predict whether these SNPs would be harmful or not. Our results suggest that the SNPs are not likely truly damaging.

Table II. Characteristics and frequencies of *CARD14* SNPs in non-familial PRP cases.

SNP	dbSNP rs#	Allele frequency in CHB control
c.1641G>C	rs2066964	G: 51%, C: 49%
c.2399-4A>G	rs11653893	A: 47%, G: 53%
c.2458C>T	rs11652075	C: 47%, T: 53%
c.2648G>A	rs2289541	G: 95%, A: 5%

CHB: Han Chinese in Beijing; SNP: single nucleotide polymorphism; dbSNP: SNP database; rs: refSNP.

## DISCUSSION

Most PRP cases are sporadic. However, familial forms with autosomal dominant or recessive inheritance have been reported. Acquired PRP usually develops in adulthood, whereas familial PRP usually presents during childhood (3–5). According to Griffiths' classification, familial PRP frequently belongs to type V (atypical juvenile) (6–8). In 2012, heterozygous mutations in *CARD14* (MIM 607211) (RefSeq NM\_024110.4) were detected in PRP after analysing 4 unrelated families with autosomal dominant PRP (2). Amino acid mutations were c.467T>C (p.Leu156Pro) and c.412\_414delGAG (p.Glu138del) which altered highly conserved amino acids. In one family, a mutation c.349+1G>A was found in the consensus donor splice site. This splice site mutation disrupted the *CARD14* splicing and caused an in-frame insertion of 66bp originating from the intron, which led to 22 amino acids insertion during the translation. Interestingly, *CARD14* mutations have also been detected in cases of familial psoriasis and correspond to PSORS2 (psoriasis susceptibility locus 2) [MIM602723] (1, 9). In the study of psoriasis, the mutations in *CARD14* included missense mutations, c.349G>A (p.Gly117Ser), c.365A>G (p.Tyr122Cys) and c.413A>C (p.Glu138Ala). One splice donor sequence mutation c.349+5G>A has also been found in a Taiwanese family. Both c.349G>A and c.349+5G>A mutations caused the same aberrant splice mRNA variant containing an extra 66bp as found in the study of familial PRP (1, 2, 10).

In this report, no phenotype-genotype associations were revealed and none of the detected polymorphisms alone were pathogenic. A genetic dosage effect is also not seen. Other gene mutations and environmental factors may interact and result in the sporadic PRP phenotype. Furthermore, none of our cases belonged to type V, while a significant portion of familial PRP were reported as type V in the literature and *CARD14*

mutations were only reported in familial patients (2, 6–8). Therefore, it is possible that different mutations exist in different types of PRP.

In summary, we found no definite causative genetic mutation in *CARD14* as identified in familial PRP after screening 8 non-familial patients of type I, type III and type IV PRP. The pathogenic mutation for non-familial non-type V PRP is still elusive.

*The authors declare no conflict of interest.*

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