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Association of -619C/T polymorphism in CDSN gene and psoriasis risk: a meta-analysis

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ABSTRACT. Previous studies investigating the association between corneodesmosin (CDSN) polymorphisms and psoriasis risk have provided inconsistent results. The aim of our study was to clarify the effects of CDSN -619C/T polymorphism on psoriasis risk by conducting a meta-analysis. We conducted searches of the published literature in Pubmed and Embase databases up to October 2010. Six studies with a total of 842 psoriasis cases and 981 healthy controls were retrieved. Statistical analysis was performed with the programs Review Manager (version 5.0.24) and Stata (version 9.2). Meta-analysis results showed that there was no significant difference in CDSN -619C/T genotype distribution between psoriasis and control in the comparisons of C allele *vs* T allele, CC *vs* CT + TT, CC + CT *vs* TT, CC *vs* TT, and CC *vs* CT (respectively: OR = 1.28, 95%CI = 0.82-2.00, P = 0.28; OR = 1.33, 95%CI = 0.80-2.21, P = 0.28; OR = 1.23, 95%CI = 0.80-1.91, P = 0.35; OR = 1.41, 95%CI = 0.64-3.12, P = 0.40; OR = 1.30, 95%CI = 0.81-2.06, P = 0.27). In the subgroup analysis by ethnicity, results also showed no significant association between

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CDSN -619C/T polymorphism and susceptibility to psoriasis in both Caucasian and Asian populations. In conclusion, this meta-analysis suggests that CDSN -619C/T polymorphism may not be associated with susceptibility to psoriasis.

Key words: Corneodesmosin; Psoriasis; Gene polymorphism; Risk; Meta-analysis

INTRODUCTION

Psoriasis is a frequent, inflammatory disease of skin and joints with considerable morbidity, characterized by epidermal hyperplasia, altered epidermal maturation, and local accumulation of acute and chronic inflammatory cells (Krueger et al., 1990; Zenz et al., 2005). The prevalence of psoriasis is estimated to be between 1.5 and 3% in Europeans, with men and women equally affected (Griffiths and Barker, 2007). However, the prevalence of psoriasis is only 0.3% of the general population in China (Griffiths and Barker, 2007). Although the pathogenesis of psoriasis is poorly understood, it is well recognized that genetic factors underlie psoriasis susceptibility (Capon et al., 2002). Over the past 10 years, a large number of research studies have investigated the molecular genetic basis and have made substantial advances in our understanding of the genetics and pathomechanisms of psoriasis (Asumalahti et al., 2000; O'Brien et al., 2001; Hui et al., 2002). Multiple genome-wide linkage and an increasing number of association studies have been carried out, leading to multiple linkage peaks and the identification of potential low-risk variants (Liu et al., 2007). However, the functional relationships between predisposing genetic variation and psoriasis risk are unclear. The corneodesmosin (CDSN) gene has been previously implicated in psoriasis pathogenesis, which is currently recognized as the marker conferring the highest psoriasis risk (Capon et al., 2003). The CDSN gene, which is 160 kb from HLA-C, has been proposed as a candidate gene in psoriasis as it is the only PSORS1 transcript to be expressed in well-differentiated keratinocytes, and is responsible for corneocyte adhesion and desquamation (Ahnini et al., 1999; Schmitt-Egenolf et al., 2001; Butt et al., 2005). The most common variant, CDSN -619C/T, has also been widely investigated in psoriasis.

Meta-analysis can be a useful tool in detecting an association that could otherwise remain masked in the sample size studies, especially in those evaluating rare allele frequency polymorphisms (Attia et al., 2003). The use of the meta-analysis has recently become an important part of genetic research mainly to reconcile previously conducted studies that gave inconsistent results. The aim of this meta-analysis was to investigate the association between CDSN -619C/T polymorphism and susceptibility to psoriasis by conducting a meta-analysis of all eligible case-control studies published to date.

MATERIAL AND METHODS

Literature search strategy

Pubmed and Embase databases were searched by two reviewers (Yan Wu and Bin Wang) to retrieve papers linking CDSN -619C/T polymorphism and susceptibility to psoriasis

published up to October 2010 without language restrictions, using the following key words: "corneodesmosin", "CDSN", "polymorphism", "polymorphism, single nucleotide", "polymorphism, genetic" and "psoriasis". The reference lists of major textbooks, review articles, and included articles were identified through manual searches to find other potentially eligible studies.

Inclusion and exclusion criteria

To be eligible for inclusion in this meta-analysis, the following criteria were established: i) case-control studies that addressed psoriasis cases and healthy controls; ii) studies on the association of CDSN -619C/T polymorphism and susceptibility to psoriasis; iii) studies that included sufficient genotype data for extraction; iv) and healthy controls were in Hardy-Weinberg equilibrium (HWE). The exclusion criteria were as follows: i) not case-control studies that evaluated the association between CDSN -619C/T polymorphism and psoriasis risk; ii) case reports, letters, reviews, meta-analysis and editorial articles; iii) studies that were based on incomplete raw data and those with no usable data reported; iv) duplicate data were included in the studies; v) family-based design was used; vi) and healthy controls were not in HWE.

Data extraction

Using a standardized form, data from published studies were extracted independently by two reviewers (Y. Wu and B. Wang) to populate the necessary information. Disagreements were resolved by discussion. From each of the articles included the following information was extracted: first author, year of publication, country, nationality, study design, sample, source of controls, number of patients and controls, detection methods, polymorphisms of gene and evidence of HWE. In the case of conflicting evaluations, an agreement was reached following a discussion.

Quality assessment of studies included

The quality of papers was also independently assessed by two reviewers (Yan Wu and Bin Wang) based on the STROBE quality score systems (Vandenbroucke et al., 2007). Thirty items relevant to the quality appraisal were used for assessment in this meta-analysis. Quality scores ranged from 0 to 30. We defined 10, 20 and 30 scores as low, moderate and high grade, respectively. Any discrepancies between the two reviewers were resolved by discussion and consultation with a third reviewer (Yuan-Hong Li).

Statistical analysis

All analyses were conducted by the Review Manager version 5.0.24 (provided by The Cochrane Collaboration) and STATA package version 9.2 (Stata Corporation, College Station, USA). The following contrasts for CDSN -619C/T polymorphism were evaluated: the comparison of variant allele with wild allele (C allele *vs* T allele); the comparison of each homozygote with the other combined with heterozygote (CC *vs* CT + TT; TT *vs* CC + CT), the comparison of variant homozygote with heterozygote and wild homozygote (CC *vs* TT; CC *vs* CT). The strength of the associations between psoriasis risk and CDSN -619C/T polymorphism was estimated by the odds ratio (OR) and 95% confidence interval (95%CI). Between-

study heterogeneities were estimated using the Cochran's *Q* test (Higgins and Thompson, 2002; Zintzaras and Loannidis, 2005). When a significant *Q* test ($P < 0.10$) indicated heterogeneity across studies, the random effects model was used for meta-analysis, or else the fixed effects model was used. We also quantified the effect of heterogeneity by using a recently developed measure, i.e., $I^2 = 100\% \times (Q - df) / Q$. I^2 ranges between 0 and 100% and represents the proportion of inter-study variability that can be attributed to heterogeneity rather than chance. I^2 values of 25, 50 and 75% were defined as low, moderate and high estimates, respectively. We tested whether genotype frequencies of controls were in HWE using the χ^2 test. Subgroup analysis based on nationality was used to explore and to explain the diversity among the results of different studies. Sensitivity analysis was mainly performed by sequential omission of individual studies. The effect of publication bias was determined by a funnel plot where the standard error of log (OR) of each study was plotted against its log (OR). An asymmetric plot indicated possible publication bias. Due to the limitations of funnel plotting, which requires a range of studies with varying sizes and subjective judgments, we evaluated publication bias using the Egger's linear regression test (Peters et al., 2006), which determines funnel plot asymmetry using a natural logarithm scale of OR. Statistical significance was considered when the P value of Egger's test was <0.05. To ensure the reliability and the accuracy of the results, two reviewers (Yan Wu and Bin Wang) populated the data in the statistic software programs independently and got the same results.

RESULTS

Studies included in the meta-analysis

The search strategy retrieved 51 potentially relevant studies. According to the inclusion criteria, 6 studies with full-text were included in this meta-analysis (Ahnini et al., 1999; Asumalahti et al., 2000; Orrù et al., 2002; Romphruk et al., 2003; Ameen et al., 2005; Chang et al. 2006) and 45 studies were excluded. The flow chart for the study selection is summarized in Figure 1. These 6 case-control studies selected included a total of 842 psoriasis cases and 981 healthy controls. All studies were case-control studies that evaluated the association of CDSN -619C/T polymorphism and susceptibility to psoriasis. The publication year of the included studies ranged from 1999 to 2006. All articles were written in English. The source of controls was based on healthy populations. The HWE test was performed on genotype distribution of the controls, and all of them were in HWE ($P > 0.05$). The baseline characteristics and methodological quality of the included studies are summarized in Table 1. The genotype distribution and risk allele frequency are summarized in Table 2.

Main results, subgroup and sensitivity analysis

A summary of the meta-analysis findings of the association between CDSN -619C/T polymorphism and psoriasis is provided in Table 3. Meta-analysis results identified that there was no significant difference in CDSN -619C/T genotype distribution between psoriasis and control in the comparisons of C allele *vs* T allele, CC *vs* CT + TT, CC + CT *vs* TT, CC *vs* TT and CC *vs* CT (respectively: OR = 1.28, 95%CI = 0.82-2.00, P = 0.28; OR = 1.33, 95%CI = 0.80-2.21, P = 0.28; OR = 1.23, 95%CI = 0.80-1.91, P = 0.35; OR = 1.41, 95%CI = 0.64-3.12,

P = 0.40; OR = 1.30, 95%CI = 0.81-2.06, P = 0.27) (Figure 2). In the subgroup analysis based on ethnicity, the included studies were divided into Caucasian and Asian populations, and the results also showed no significant association between CDSN -619C/T polymorphism and susceptibility to psoriasis in both Caucasian and Asian populations.

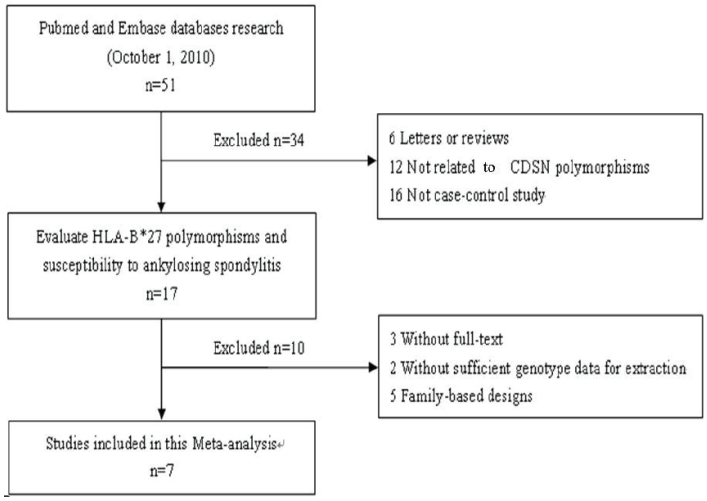

Figure 1. Flow chart showing study selection procedure.

Table 1. Baseline characteristics of studies included in meta-analysis.

First author (year)	Country	Ethnicity	Source of controls	Sample	Detection method	Number of subjects		Quality score
						Cases	Controls	
Ahnini et al. (1999)	England	Caucasian	Population-based	Blood	PCR	235	374	19
Asumalahti et al. (2000)	Finland	Caucasian	Population-based	Blood	PCR	100	93	18
Orrù et al. (2002)	Italy	Caucasian	Population-based	Blood	PCR	147	120	24
Romphruk et al. (2003)	Thailand	Asian	Population-based	Blood	PCR	139	144	22
Ameen et al. (2005)	Japan	Asian	Population-based	Blood	PCR-SSP	43	47	21
Chang et al (2006)	China	Asian	Population-based	Blood	PCR	178	203	23

PCR = polymerase chain reaction; PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism.

Table 2. Genotype distribution and risk allele frequency of all studies included.

First author (year)	Genotype distribution								HWE test	
	Cases				Controls					
	CC	CT	TT	C (frequency)	CC	CT	TT	C (frequency)	$\chi 2$	P value
Ahnini (1999)	178	53	4	0.870	283	85	6	0.870	0.018	0.893
Asumalahti (2000)	74	24	2	0.860	67	24	2	0.850	0.008	0.928
Orrù (2002)	94	47	6	0.800	79	37	4	0.810	0.026	0.871
Romphruk (2003)	112	25	2	0.890	68	62	14	0.686	0.004	0.952
Ameen (2005)	23	17	3	0.733	21	21	5	0.676	0.020	0.888
Chang (2006)	77	80	21	0.657	95	88	20	0.685	0.003	0.953

No. = number of subjects; HWE = Hardy-Weinberg equilibrium.

Table 3. Meta-analysis of the association between CDSN -619C/T polymorphism and psoriasis risk.

Comparison	OR	95% CI	P value	Heterogeneity		Effects model
				I^2	P value	
C allele vs. T allele	1.28	0.82-2.00	0.28	84%	<0.00001	Random
Caucasian	0.99	0.78-1.26	0.93	0%	0.89	
Asian	1.66	0.62-4.42	0.31	93%	<0.00001	
CC vs. CT + TT	1.33	0.80-2.21	0.28	83%	<0.0001	Random
Caucasian	1.00	0.76-1.31	0.98	0%	0.91	
Asian	1.79	0.58-5.54	0.31	93%	<0.00001	
CC + CT vs. TT	1.23	0.80-1.91	0.35	35%	0.17	Fixed
Caucasian	0.91	0.40-2.06	0.81	0%	0.97	
Asian	1.39	0.83-2.33	0.21	73%*	0.03*	
CC vs. TT	1.41	0.64-3.12	0.40	56%	0.04	Random
Caucasian	0.90	0.39-2.07	0.81	0%	0.96	
Asian	2.31	0.44-12.01	0.32	82%	0.004	
CC vs. CT	1.30	0.81-2.06	0.27	78%	0.0004	Random
Caucasian	1.00	0.76-1.33	0.98	0%	0.93	
Asian	1.70	0.61-4.77	0.31	89%	0.0001	

* = using random effects model; OR = odds ratio; 95%CI = 95% confidence interval.

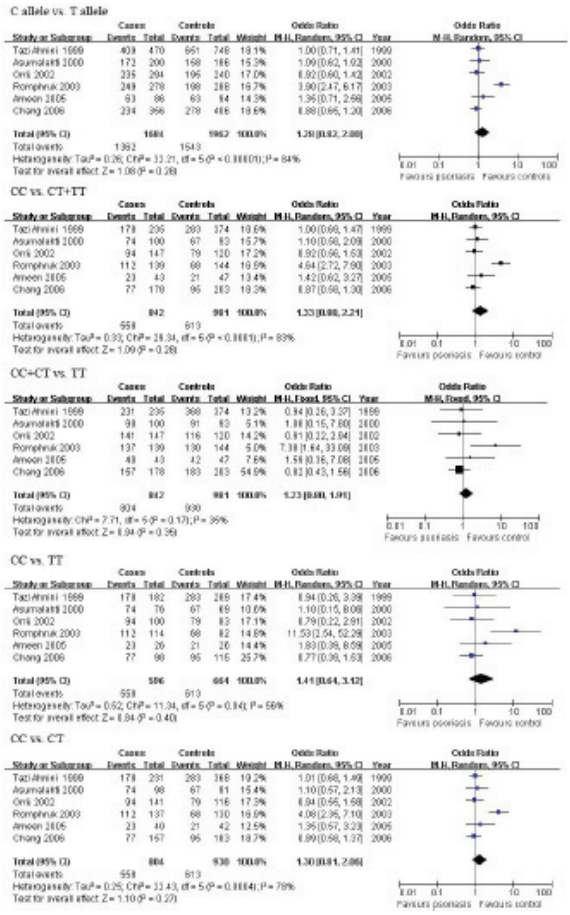

Figure 2. Forest plot of psoriasis risk associated with CDSN -619C/T polymorphism.

Significant heterogeneity between studies was observed in the comparisons of C allele *vs* T allele, CC *vs* CT+TT, CC *vs* TT and CC *vs* CT with the *Q* test and the I^2 test (P < 0.1, $I^2 \geq$ 50%). Therefore, the random effects model was used to pool the results. Sensitivity analysis was performed by sequential omission of individual studies. However, the significance of pooled OR under fixed and random models in all individual analyses and subgroup analyses was not substantially influenced by omitting any single study.

Publication bias

Publication bias of the studies was assessed by Begg's funnel plot and Egger's test. The publication bias of the meta-analysis on the association between CDSN -619C/T polymorphism and susceptibility to psoriasis was detected in the comparison of C allele *vs* T allele. The funnel plots of the 6 studies appeared to be symmetrical. Egger's test also showed that there was no statistical significance for the evaluation of publication bias (t = 0.83, P = 0.455, 95% CI = -0.839-1.552) (Figure 3).

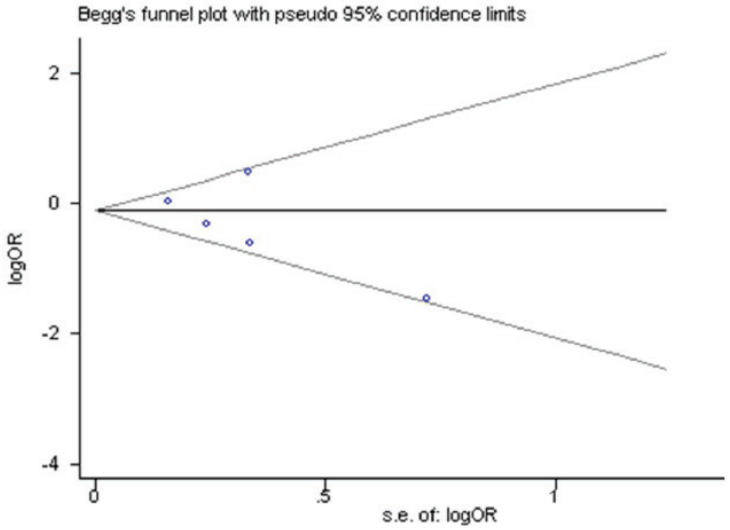

Figure 3. Evaluation of publication bias.

DISCUSSION

The cutaneous lesions of psoriasis are characterized by epidermal hyperproliferation, abnormal keratinocyte differentiation, and infiltration of T cells, neutrophils and other mononuclear cells (Terui et al., 2000). Although the pathogenesis of psoriasis remains elusive, molecular genetics analyses have identified PSORS1, near HLA-C, to be the major genetic determinant of psoriasis (Chang et al., 2003). Among these possible candidate genes near HLA-C, the CDSN and HCR genes have recently drawn much attention. The CDSN gene located only 160 kb telomeric of HLA-C encodes a desmosomal protein involved in corneocyte cohesion, whose proteolysis may contribute to desquamation (Guerrin et al., 1998). The product of the

CDSN gene, corneodesmosin, is a glycoprotein secreted by granular keratinocytes and incorporated into the desmosomes, and the degradation of corneodesmosin is considered to be essential for normal desquamation to occur (Caubet et al., 2004).

Many research studies have evaluated the association of CDSN -619C/T polymorphism and psoriasis risk, but the results are controversial. Our meta-analysis quantitatively assessed the association between CDSN -619C/T polymorphism and susceptibility to psoriasis. Finally, 6 case-control studies were included and assessed, involving a total of 842 psoriasis cases and 981 healthy controls. The main meta-analysis results showed that there was no significant difference in CDSN -619C/T genotype distribution between psoriasis and control in the comparisons of C allele *vs* T allele, CC *vs* CT + TT, CC + CT *vs* TT, CC *vs* TT and CC *vs* CT, which indicated that there may be no association between CDSN -619C/T polymorphism and psoriasis risk. In the subgroup analysis by ethnicity, no significant association was found as well between CDSN -619C/T polymorphism and susceptibility to psoriasis in all comparisons. Results showed obvious heterogeneity between studies, suggesting a possible role of ethnic differences in genetic backgrounds and the environment in which they lived. There was no evidence of publication bias in this meta-analysis. As the eligible study number was small in this meta-analysis of CDSN -619C/T polymorphism, these results still need further investigation.

Some limitations of our meta-analysis should be addressed. First, because of incomplete raw data, some relevant studies could not be included in our analysis. Secondly, the number of published studies was not sufficiently large for a comprehensive analysis, and some included studies of small size might not have had enough statistical power to explore the real association between CDSN -619C/T polymorphism and susceptibility to psoriasis. Finally, our systematic review was based on unadjusted data, as the genotype information stratified for the main confounding variables was not available in the original papers and since the confounding factors addressed across the different studies were also variable.

In conclusion, our meta-analysis of 6 case-control studies demonstrated that CDSN -619C/T polymorphism may not be associated with susceptibility to psoriasis. Few studies are available in this field and current evidence remains limited. Therefore, it should be emphasized that there is a need to conduct large studies with an adequate methodological quality, properly controlling for possible confounds in order to obtain valid results.

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