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Original Article

Association of *CRR9* locus with elevated risk of squamous cell carcinoma and basal cell carcinoma

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Abstract: Background: Published studies have generated inconsistent results related to the contribution of *CRR9* rs401681 C allele to the risk of developing non-melanoma skin cancer (NMSC), and it is the inconsistency that promoted us to undertake a meta-analysis to identify the degree of impact the C allele has on NMSC. Method: The PubMed, Science Direct, Embase and Cochrane Library were thoroughly searched from the start of November 2013 to the end of April 2014 by using *CRR9*, polymorphism, skin cancer and their synonyms. Based on a total of 44,036 subjects, we calculated ORs and 95% CIs to measure the influence of the C allele on NMSC predisposition. Results: Overall, individuals carrying the risk C allele at rs401681 had 1.16 times (OR = 1.16, 95% CI: 1.10-1.21, heterogeneity: $P = 0.298$ and $I^2 = 0.166$, **Figure 2**) greater risk of NMSC compared to the common T allele. In the further stratified analyses, we found a significant association between the C allele and BCC, Icelanders, and non-Icelanders. Conclusion: The results of this meta-analysis suggest that the C allele at rs401681 is likely to modify the genetic predisposition to NMSC.

Keywords: Genetic risk, non-melanoma skin cancer, *CRR9*

Introduction

Telomeres mapping on the ends of human chromosomes facilitate chromosomal fusions, destruct genome integrity, and enable rearrangements by inhibiting the encoding of sequence erosion and subsequent reconstruction of DNA breakage [1, 2]. The highly conserved repetitive DNA sequences also interact with conventional semiconservative replication and ensures sequence completeness at each end of the telomeres during replication consequently [3]. The evolution of many malignant cells in solid tumors is markedly linked with progressively shorter telomere that promotes cellular proliferation and induces p53-dependent G1/S cell cycle arrest, leading to irreversible DNA damage [4]. Telomerase encoded by telomerase reverse transcriptase (*TERT*) acts in a vast majority of human cancers (85%-90%). *TERT* along with cleft lip and palate transmembrane 1-like (*CRR9*, *CLPTM1L*) located at 5p15.33 locus controls telomere synthesis and maintains telomere length in normal conditions. Since a *CRR9*-encoded transcript is overexpressed in cisplatin-resistant-sensitive cells and this overexpression triggers apoptotic activities [5-8], *CRR9* has therefore been presumed to regulate apoptosis in protection against cisplatin-stimulated genotoxic stress.

A panel of genome-wide association studies (GWAS) have provided new insights for the genetic predisposition field and showed that the genes at 5p15.33 chromosome are ideal association signals [9-13]. A well-known C to T single nucleotide polymorphism (SNP) in the *CRR9* region has been the focus of extensive research and an increasing body of literature has detected a clear connection with various types of cancer [14-16]. A recent meta-analysis of melanoma and rs401681 supported a significantly reduced melanoma rate related to the C allele [17]. We thus hypothesized that the

rates of base cell carcinoma (BCC) and squamous cell carcinoma (SCC), two major phenotypes of non-melanoma skin cancer (NMSC, corresponds to BCC and SCC thereafter), may be influenced by the same allele. To test the hypothesis, we carried out a meta-analysis combining all previous epidemiological reports which have produced mixed conclusions [18, 19], in an attempt to determine the role of the C allele played in incidence of NMSC.

Methods and materials

This study was undertaken in agreement with PRISMA statement proposed by Moher and comates [20].

Identification and eligibility of relevant studies

A comprehensive literature search of the PubMed database was performed by combining "*CRR9*", "polymorphism", "skin cancer" and their synonyms from the start of November 2013 to the end of April 2014 to retrieve the potentially relevant studies. To identify additional information, we thoroughly searched the Science Direct, Embase and Cochrane Library from January 10 to April 30, 2014 and scanned the references of all papers identified through databases. No restrictions were used during the searches to minimize the likelihood of biased results.

Eligible studies were selected based on the criteria including:

1 Reporting on the association between *CRR9* rs401681 and NMSC;

2 Defined as a case-control or nested case-control study;

3 Providing detailed information on genotype frequency or at least the allele frequency;

As the patient series in the study by Rafnar et al. [13] was updated by Stacey et al. [18], we thus selected the new study due to the larger sample size.

Data extraction

Data covering the last name of first author, study design, total patients and controls, country of study, ethnicity, allele rates in patients and controls, number of genotypes or alleles, histological type, and publication year were extracted in duplicate by. A total of six unrelated populations included in a multi-center study were taken as independent studies during meta-analysis [18]. The Caucasian descendants were categorized as non-Icelanders or Icelander according to the country where they resided. An expert in this field was invited in case of disparities.

Statistical analyses

All statistical tests were two-sided and P <.05 was considered significant. The crude OR and 95% CI (odds ratio and 95% confidence interval) was combined by using the fixed or random effects meta-analysis to evaluate the strength of association between the C allele at *CRR9* locus and NMSC risk (C versus T). Inter-study heterogeneity was detected by a Chi square-based Q-test and P less than .05 was judged as the significance level. Variance between studies was also measured by I^2 statistic, with higher proportion indicating larger heterogeneity (I^2 < 25%, 25%-75%, > 75% corresponds to low, moderate and large heterogeneity, respectively) [21]. In case of P >. 05 and I^2 < 50% which represented no, low or moderate heterogeneity, we performed the fixed effects meta-analysis proposed by Mantel and Haenszel to combine the genetic effects [22]; conversely, the random effects meta-analysis proposed by DerSimonian and Laird was more suitable [23]. Subgroup analyses were performed according to histological type and ethnicity. Publication bias was diagnosed by constructing a funnel plot and performing the Egger's liner regression test to further examine whether the single studies were symmetrically distributed in the funnel plot [24]. We also performed the leave-one-out sensitivity analyses to check if the combined estimations remained stable when sequentially deleting the single studies. Analyses were done by using the software Stata (Version 12.0; Stata corporation, College Station, Texas, USA) and R software, version 3.0.3 (the R Foundation for Statistical Computing).

Results

Study characteristics

Searches of aforementioned databases yielded thirty-one papers. We evaluated all titles and

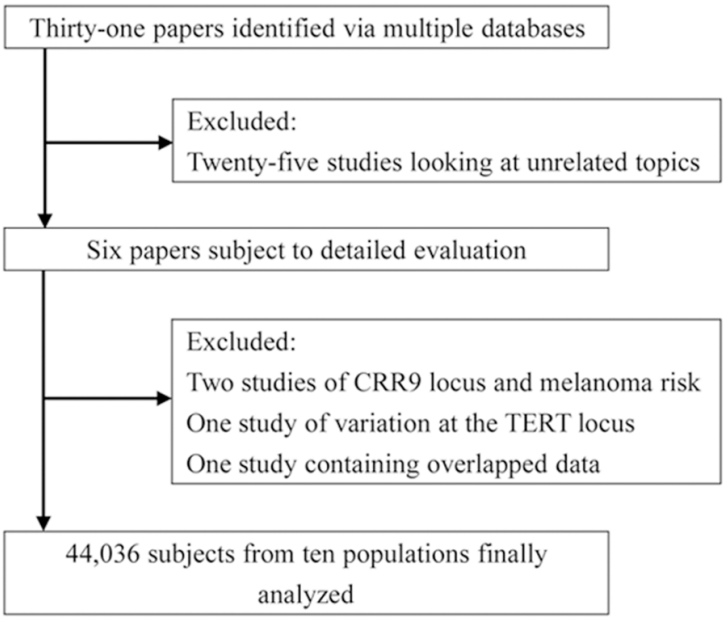

Figure 1. Study flow-chart illustrating the literature search and eligible study selection process.

abstracts and eliminated twenty-five studies due to research unrelated to the current subject. The six remainders were evaluated in detail and four were discarded due to research on variation at the *TERT* locus [25], *CRR9* locus and melanoma risk [17, 26], and overlapped data [13]. Two papers, providing 8 unrelated populations with 5,120 patients and 38,916 controls, were eventually included in the meta-analysis [18, 19] (**Figure 1**). These populations of Caucasian ethnicity consisted of two Icelander populations and six non-Icelander populations from various countries including the United States, Eastern Europe, and Spain. There are five BCC studies and three SCC studies. The risk allele frequency in cases and controls was similar across the studies (case: 0.55-0.60, control: 0.54-0.57). The specific information is presented in **Table 1**.

Quantitative data synthesis

In the analysis of total subjects, as shown in **Table 2**, compared to the common T allele, individuals carrying the risk C allele at rs401681 had 1.16 times (OR = 1.16, 95% CI: 1.10-1.21, heterogeneity: $P = 0.298$ and $I^2 = 0.166$, **Figure 2**) higher risk of NMSC.

Stratification analysis by histological type showed moderately elevated risk of BCC among the C allele carriers (OR = 1.19, 95% CI: 1.13-1.26, heterogeneity: $P = 0.527$ and $I^2 = 0$, **Figure 3**). In the subsequent stratified analysis according to ethnicity, we found significant associations in both Icelanders and non-Icelanders; the association seemed stronger in Icelanders (OR = 1.17, 95% CI: 1.04-1.32, heterogeneity: $P = 0.103$ and $I^2 = 0.623$) and relatively weaker in non-Icelanders (OR = 1.10, 95% CI: 1.03-1.18, heterogeneity: $P = 0.738$ and $I^2 = 0$, **Table 2**).

Sensitivity analysis

Sensitivity analysis is widely acceptable method used to detect the impact of studies included in meta-analysis on the overall estimates, with materially altered effect estimates representing instability of the results. No significant changes were seen in the pooled ORs when deleting the studies (one at a time) incorporated in our meta-analysis, suggesting our results are stable and reliable (data not shown).

Bias diagnostics

As shown in **Figure 4**, the independent studies in the funnel plot were symmetrically distributed. To confirm the symmetry, we performed the Egger's test and found no evidence of obvious publication bias in the study (Egger: $P = 0.317$).

Discussion

In this work, we undertook a meta-analysis combining data from molecular epidemiology studies on rs401681 polymorphism in the *CRR9* region and NMSC risk in order to derive more precise effect estimation. A total of 44,036 subjects were analyzed and we found 1.16 times elevated risk of NMSC in relation to the C allele when all data were pooled into one dataset. A slightly higher risk of BCC (OR = 1.19), rather than SCC, was observed when data were stratified by ethnicity. We also observed a marginally stronger association between the C allele and NMSC risk in Icelanders (OR = 1.17) and the association seemed to be relatively weaker in non-Icelanders (OR = 1.10).

Table 1. Published studies included in meta-analysis

First author (reference)	Year	Histological type	Sample		Frequency (C/T)		Population
			Cases	Controls	Cases	Controls	
Nan	2011	Squamous cell carcinoma	266	809	0.58/0.42	0.57/0.43	Caucasian (non-Icelander)
Nan	2011	Basal cell carcinoma	283	809	0.60/0.40	0.57/0.43	Caucasian (non-Icelander)
Stacey-Iceland	2009	Basal cell carcinoma	1850	34998	0.60/0.40	0.55/0.45	Caucasian (Icelander)
Stacey-Eastern Europe	2009	Basal cell carcinoma	525	525	0.62/0.38	0.57/0.43	Caucasian (non-Icelander)
Stacey-US	2009	Basal cell carcinoma	908	826	0.59/0.41	0.56/0.44	Caucasian (non-Icelander)
Stacey-Spain	2009	Basal cell carcinoma	185	1758	0.55/0.45	0.54/0.46	Caucasian (non-Icelander)
Stacey-Iceland	2009	Squamous cell carcinoma	438	34998	0.57/0.43	0.55/0.45	Caucasian (Icelander)
Stacey-US	2009	Squamous cell carcinoma	665	826	0.57/0.43	0.56/0.44	Caucasian (non-Icelander)

Table 2. Meta-analysis for the association of *CRR9* locus and NMSC risk

Genetic model tested	Variables	Cases/controls	OR (95% CI)	Test of heterogeneity		Calculation of ORs
				P	I^2	
C versus T	Total	5,120/38,916	1.16 (1.10, 1.21)	0.298	0.166	Fixed-effects
	Histological type					
C versus T	Basal cell carcinoma	3,751/38,916	1.19 (1.13, 1.26)	0.527	0	Fixed-effects
C versus T	Squamous cell carcinoma	1,369/36,633	1.06 (0.97, 1.16)	0.915	0	Fixed-effects
	Ethnicity					
C versus T	Icelanders	2,288/34,998	1.17 (1.04, 1.32)	0.103	0.623	Random-effects
C versus T	Non-Icelanders	2,832/3,918	1.10 (1.03, 1.18)	0.738	0	Fixed-effects

The significant associations revealed in the current analysis seem reasonable. Telomerase previously described as an important anticancer mechanism which prevents malignant cells from proliferating and promotes apoptosis are a class of end-point enzymes fundamental in protecting chromosomes from genomic instability in embryonic stem cells and progenitor cells from initially inactivated intact stem cells; in most human cells, however, the enzymes do not function and remains inactive, leading to uncontrolled cell growth and inhibited apoptosis [27-29]. Rafnar et al. recently reported that the variations at rs401681, a well-characterized variant located in a linkage disequilibrium block embracing both *TERT* and *CRR9*, enable the formation of DNA adducts and stimulate the activation of metabolites [13]; in the same report, the authors demonstrated that dysfunction of telomerase is involved in the malignant progression of many human tissues, thus inducing various invasive cancers, such as cancers of breast, lung, ovary and cervix, and skin [13]. The contribution of rs401681 has been examined in a recent analysis of several types of cancer and the investigators found statistically significantly increased risk in carriers who harbor two variant C alleles [30]. The findings in previous research, together with the evidence provided in our analysis, point to an implication that the rs401681 C allele may represent a major risk factor for the development of most human diseases.

The reported association between the variant C allele and BCC varies extensively in previous series. Stacey et al. investigated the pathological role rs401681 plays in BCC incidence in four populations from Iceland, Eastern Europe, the United States and Spain respectively and showed some evidence of a significant association in the largest population comprising of 36,848 Icelanders [18]. The original finding was not replicated by a subsequent nested case-control study of Caucasians from the United States [19]. In terms of SCC, the incidence seemed to not associate with the rs401681 C allele, because even the study with the largest number (35,436) failed to detect a major effect. In line with the first report, our study, based on all data from published reports, supported a positive association with BCC. A number of earlier candidate genes studies have also provided abundant evidence in support of a genetic linkage with BCC instead of SCC [31-33]. One of the explanations for this variation may lie in the different genetic constitution and etiological mechanism of the two subsets.

People residing in Western countries, compared to those from Asian countries, are more prone to develop skin cancer. For example, approximately 20% of American people are

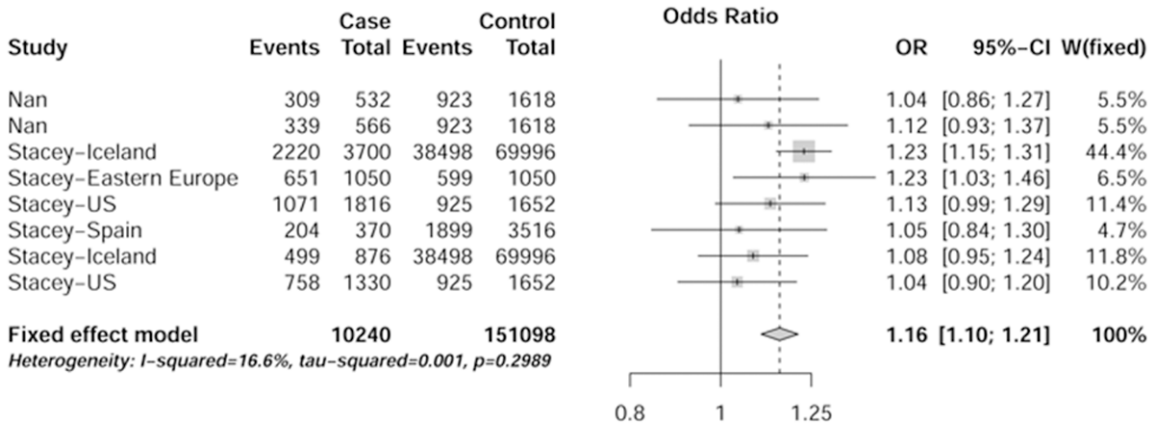

Figure 2. Estimated OR with 95% CI for NMSC risk odds ratios associated with the C allele at rs401681 in all 8 populations. The area of each square is proportional to the variance of the log OR. The combined OR and 95% CI is denoted as a diamond. The combined OR is indicated as a dotted vertical line.

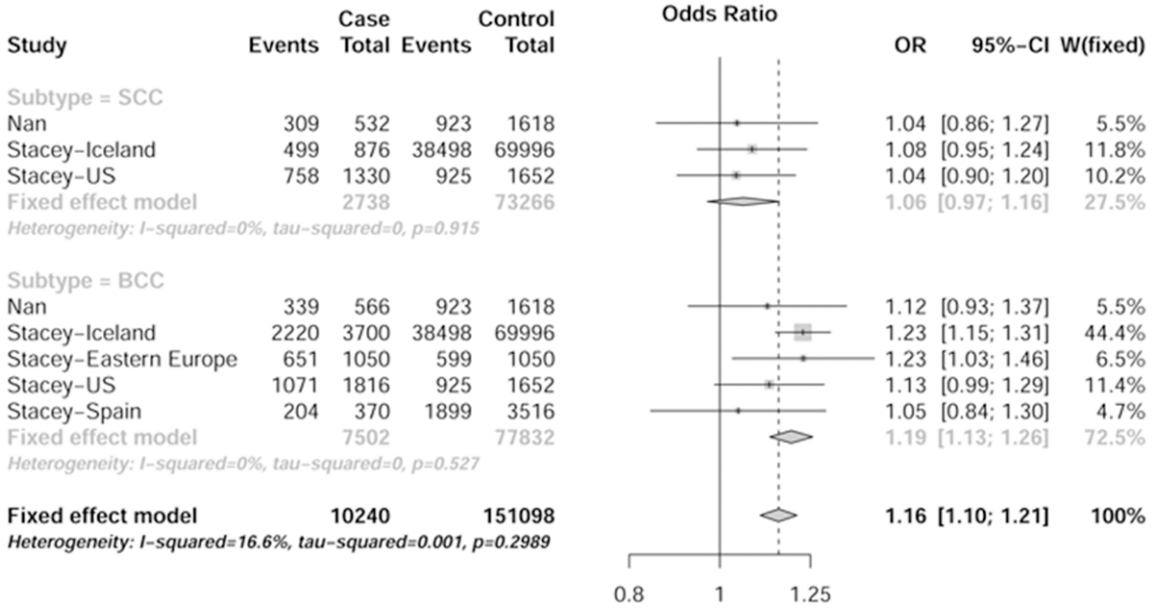

Figure 3. Stratification analysis by histological type showed moderately elevated risk of BCC among the C allele carriers.

being affected by the prevalent cutaneous cancer [34, 35]. However, skin cancer no longer favors Caucasians only and the incidence becomes increasingly higher in many parts of the world [36]. The unfavorable prevalence highlights the need for research to determine the role of rs401681 in skin cancer, such that clinicians could identify the high-risk individuals. Only Caucasians were previously studied and lack of data makes it impossible to estimate the effects in other ethnicities. The second limitation refers to the significant heterogeneity in the results for Icelanders which may result from methodological inappropriateness, study designs and sample size. The associations therefore should be interpreted with caution. Finally, ultraviolet (UV) radiation is a known carcinogenic factor for human skin cancer. It is thus tempting to speculate that UV exposure may further elevate the skin cancer risk by interacting with susceptibility genes. The combined effect is expected to be considered in future research.

In conclusion, we obtained some evidence to support a significant role of rs401681 at *CRR9*

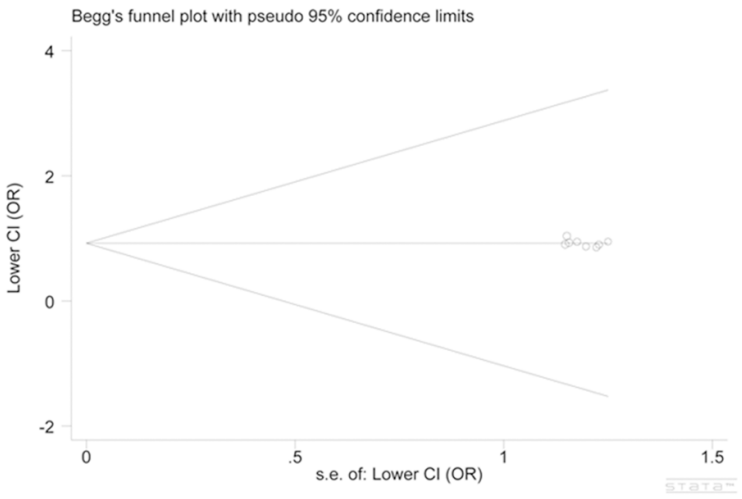

Figure 4. Funnel plot analysis to detect publication bias. Each point represents an individual study for the indicated association.

locus in NMSC and BCC predisposition. As a better understanding of the association between the *CRR9* locus and NMSC cancer susceptibility could help to identify the high risk group, a study with a large number is needed to expand the current knowledge of the mechanism that underlies genetic predisposition to NMSC.

Disclosure of conflict of interest

None.

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