RESEARCH ARTICLE

Associations Between XRCC1 Arg399Gln, Arg194Trp, and Arg280His Polymorphisms and Risk of Differentiated Thyroid Carcinoma: A Meta-analysis

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Abstract

Background: Associations between Arg399Gln, Arg194Trp and Arg280His polymorphisms of the XRCC1 gene and risk of differentiated thyroid carcinoma (DTC) have been widely studied but the findings are contradictory. Methods: We performed a meta-analysis in the present study using STATA 11.0 software to clarify any associations. Electronic literature databases and reference lists of relevant articles revealed a total of 10, 6 and 6 published studies for the Arg399Gln, Arg194Trp and Arg280His polymorphisms, respectively. Results: No significant associations were observed between Arg399Gln and DTC risk in all genetic models within the overall and subgroup meta-analyses, while the Trp/Trp vs Arg/Arg and recessive model of the Arg194Trp polymorphism was associated with DTC susceptibility, and the dominant model of Arg280His polymorphism contributed to DTC susceptibility in Caucasians. Conclusions: Our meta-analysis suggests that XRCC1 Arg194Trp may be a risk factor for DTC development.

Keywords: XRCC1 - Arg399Gln - Arg194Trp - Arg280His - differentiated thyroid carcinoma - meta-analysis

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Introduction

The majority of endocrine malignancies are thyroid cancer (TC), which accounts for more than 90% and contributes to more than 50% of all deaths from endocrine cancers (Gilfillan 2010; Aschebrook-Kilfoy et al., 2011). The exact etiology of TC remains unknown, but exposure to ionizing radiation at a young age is the best-known and only verified risk factor (Papadopoulou et al., 2008). However, most TC patients do not have a history of radiation exposure, and studies reported that gene polymorphisms including DNA repair genes influence on thyroid cancer susceptibility (Gudmundsson et al., 2012; Endrzejewski et al., 2012), genetic variations in DNA repair genes are thought to modify DNA repair capacity and related to cancer risk (Alberg et al., 2013), indicating that potential predisposing genetic factors may modify an individual's susceptibility to TC.

Most TC are differentiated thyroid carcinoma (DTC), which account for >90% of thyroid malignancies. Pathologically, DTC include papillary, follicular and Hürthle cell carcinoma. Thus far, predisposed families and association studies have revealed several genomic loci that may harbor causative genes for susceptibility of non-medullary TC (Bonora et al., 2010), suggesting a high level of genetic heterogeneity for this tumor (Khan et al., 2010).

The human genome is constantly exposed to DNA damaging agents that produce abasic sites (AP sites), base damage of different types, and single stranded breaks (SSBs) (Bont et al., 2004). Base excision repair (BER) and single strand break repair (SSBR) pathways are involved in the repair of such lesions (Zharkov 2008). Among them, BER is the predominant DNA damage repair pathway for the processing of endogenous DNA lesions and exposures to ionizing radiation (Wallace et al., 2012).

The X-ray repair cross-complementing Group1 (XRCC1) gene is 33 kb long and is located on chromosome 19q13.2–13.3 (Chou et al., 2008). It encodes an essential multidomain protein that plays a role in the BER and SSBR processes (Hanssen-Bauer et al., 2011). XRCC1 involved in the efficient repair of DNA SSBs formed by exposure to ionizing radiation and alkylating agents. Nonsynonymous single nucleotide polymorphisms (nsSNPs) of XRCC1 may affect the capacity to undergo DNA repair, which has been identified as a modifying risk factor in maintaining the genomic stability (Ming et al., 2012).

Numerous studies have investigated the potential biological significance of the three most common XRCC1 nsSNPs (Arg399Gln, Arg194Trp, and Arg280His), however, the sample sizes of these previous studies were limited and the genetic epidemiological studies into DTC risk are not conclusive. Therefore, in the present study,

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Table 1. Characteristics of Studies Included in XRCC1 Arg399Gln, Arg194Trp and Arg280His Polymorphisms and DTC Risk

Polymorphism	First author	Year	Country or region(Ethnicity)	Source of controls	Cases*	Controls*	Variant allele frequency	*P* for HWE
Arg399Gln								
	Ryu et al., 2011	2011	Korea(Asian)	Hospital-based	87/17/7	72/19/9	0.19	0.0002
	Zhu et al., 2004	2004	China(Asian)	Hospital-based	49/44/12	57/45/3	0.24	0.09
	Akulevich et al., 2009	2009	Russia and Belarus(Caucasian)	Population-based	65/53/14	158/193/47	0.36	0.3
	Sigurdson et al., 2009	2009	Kazakhstan and Ru ssia(Caucasian)	Population-based	12-10-2	460/343/89	0.29	0.04
	Chiang et al., 2008	2008	Taiwan(Asian)	Hospital-based	150/110/23	277/165/27	0.23	0.71
	Fard-Esfahani et al., 2011	2011	Iran(Caucasian)	Hospital-based	78/60/17	83/87/20	0.33	0.69
	Garcia-Quispes et al., 2011	2011	Spain(Caucasian)	Population-based	153/186/47	196/212/66	0.36	0.48
	Ho et al., 2009	2009	America(Mixed)	Hospital-based	133/99/19	220/216/67	0.35	0.23
	Siraj et al., 2008	2008	Saudi Arabia(Caucasian)	Hospital-based	35/13/2	142/72/15	0.22	0.16
	Santos et al., 2012	2012	Portugal (Caucasian)	Hospital-based	46/50/13	87/105/25	0.36	0.43
Arg194Trp								
	Ryu et al., 2011	2011	Korea(Asian)	Hospital-based	59/43/9	37/49/14	0.39	0.73
	Zhu et al., 2004	2004	China(Asian)	Hospital-based	50/52/3	48/51/6	0.3	0.11
	Chiang et al., 2008	2008	Taiwan(Asian)	Hospital-based	127/119/37	234/199/36	0.29	0.48
	Fard-Esfahani et al., 2011	2011	Iran(Caucasian)	Hospital-based	136/18/3	166/20/1	0.06	0.64
	Ho et al., 2009	2009	America(Mixed)	Hospital-based	203/45/3	433/69/1	0.07	0.31
	Santos et al., 2012	2012	Portugal(Caucasian)	Hospital-based	98-8-2	196/21/0	0.05	0.45
Arg280His								
	Garcia-Quispes et al., 2011	2011	Spain(Caucasian)	Population-based	337/58/3	426/44/3	0.05	0.12
	Ho et al., 2009	2009	America(Mixed)	Hospital-based	229/22/0	453/50/0	0.05	0.24
	AK Siraj et al., 2008	2008	Saudi Arabia(Caucasian)	Hospital-based	33-12-5	129/79/21	0.26	0.09
	NM Akulevich et al., 2009	2009	Russia and Belarus(Caucasian	)Population-based	117/15/0	366/32/0	0.04	0.4
	FY Chiang et al., 2008	2008	Taiwan(Asian)	Hospital-based	224/54/5	349/113/7	0.14	0.53
	Fard-Esfahani et al., 2011	2011	Iran(Caucasian)	Hospital-based	146/23/1	173/18/2	0.06	0.07

*Wild-type homozygote/ heterozygote/ variant homozygote

we performed a meta-analysis to quantitatively assess the associations between these three polymorphisms and genetic predisposition to DTC risk. This meta-analysis may be useful in the development of improved prevention programs and therapeutic measures.

Materials and Methods

Publication search

We searched PubMed, Springer and Web of Science databases from their earliest start dates until January 2013 for all publications about XRCC1 polymorphisms and risk of DTC. The key words were: XRCC1 polymorphisms; differentiated thyroid carcinoma; and thyroid cancer. Those papers quoted as references in the retrieved studies were also searched.

Inclusion and exclusion criteria

Studies included in this meta-analysis had to meet the following criteria: (1) a case-control or cohort design; (2) an evaluation of the associations between XRCC1 Arg399Gln, Arg194Trp, Arg280His polymorphisms and DTC risk; and (3) presentation of sufficient genotype data to estimate the odds ratio (OR) and 95% confidence interval (CI). We excluded those studies that did not report genotype frequency. When the same population was included in different articles, the article with the largest population of participants or the one containing more useful information was included.

Data extraction

Data were carefully and independently extracted from the relevant papers by two of the authors (YD and LH) using the same standardized form. In case of disagreement, a third reviewer assessed the articles until an agreement was reached. The following items were collected from each article: first author, publication year, country or region, ethnicity, source of controls, the genotype between cases and controls.

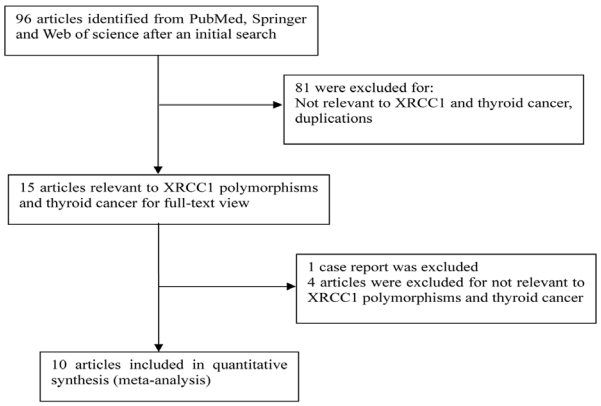

Figure 1. Flow Diagram of the Study Selection Process

Statistical analysis

The meta-analysis was performed by STATA11.0 software (v.11.0; Stata Corporation, College Station, TX). The strength of the associations between DTC and XRCC1 polymorphisms was estimated using ORs with corresponding 95% CIs. Hardy-Weinberg equilibrium (HWE) was calculated for each study control using a goodness-of-fit test (chi-square or Fisher's exact test), and $P<0.05$ was considered a significant disequilibrium. The pooled ORs were performed for a codominant model, a dominant model, and a recessive model.

Heterogeneity among studies was evaluated by I^2 (Higgins et al., 2003). When I^2 was less than 50%, the studies were considered to have acceptable heterogeneity and the fixed-effects model with the Mantel-Haenszel method was used. Alternatively, a random effect model with the DerSimonian and Laird (DL) method was used. Sensitivity analyses were also performed to assess the stability of the results. The influence of each study on the pooled estimate was assessed by omitting one study

Table 2. Results of the meta-analysis on XRCC1 Arg399Gln, Arg194Trp and Arg280His polymorphisms and DTC risk

Polymorphism	No.	Variant homozygote vs. wild-type homozygote			Heterozygote vs. wild-type homozygote			Dominant model			Recessive model		
		OR(95% CI)	I^2 (%)	Egger's test *P*	OR(95% CI)	I^2 (%)	Egger's test *P*	OR(95% CI)	I^2 (%)	Egger's test *P*	OR(95% CI)	I^2 (%)	Egger's test *P*
Arg399Gln													
Overall	10	0.88(0.71-1.10)	43.7	0.64	0.93(0.81-1.06)	20.2	0.41	0.92(0.81-1.04)	43	0.6	0.91(0.74-1.13)	30.9	0.5
Asian	3	1.56(0.63-3.86)	63.1	0.88	1.14(0.88-1.47)	0	0.33	1.19(0.93-1.51)	34.6	0.56	1.50(0.64-3.51)	59.2	0.84
Caucasian	6	0.86(0.65-1.14)	0	0.33	0.90(0.75-1.07)	10.5	0.46	0.89(0.75-1.05)	0	0.44	0.90(0.69-1.18)	0	0.71
HWE in controls	8	0.94(0.64-1.36)	55.1	0.5	0.93(0.81-1.07)	34.7	0.34	0.91(0.74-1.11)	53.3	0.61	0.93(0.75-1.15)	44.8	0.33
Hospital based	7	0.96(0.58-1.59)	61.5	0.57	0.91(0.77-1.08)	14.2	0.5	0.90(0.71-1.14)	50.7	0.71	1.0(0.64-1.56)	53.2	0.53
Population based	3	0.85(0.60-1.21)	0	0.75	0.93(0.63-1.36)	51.8	0.85	0.94(0.75-1.16)	44.4	0.85	0.86(0.62-1.20)	0	0.85
Arg194Trp													
Overall	6	1.42(0.55-3.67)	65.1	0.82	1.03(0.85-1.26)	31.2	0.29	1.04(0.78-1.39)	51	0.35	1.42(0.62-3.23)	56.8	0.76
Exclude Ri A R y u'study	5	1.87(1.20-2.90)	33.8	0.63	1.12(0.91-1.38)	0	0.36	1.21(0.99-1.48)	0	0.39	1.79(1.17-2.74)	33.5	0.61
Arg280His													
Overall	6	1.0(0.51-1.96)	0	0.59	1.06(0.75-1.51)	62.3	0.84	1.07(0.77-1.47)	58.5	0.78	1.08(0.56-2.10)	0	0.24
Caucasian	4	0.95(0.42-2.16)	0	0.77	1.28(0.83-1.96)	51.6	0.34	1.32(1.01-1.73)	47	0.42	1.03(0.46-2.33)	0	0.46
Hospital based	4	0.96(0.46-2.0)	0	0.41	0.83(0.65-1.07)	32.5	0.67	0.85(0.66-1.08)	12.9	0.57	1.06(0.51-2.20)	0	0.21

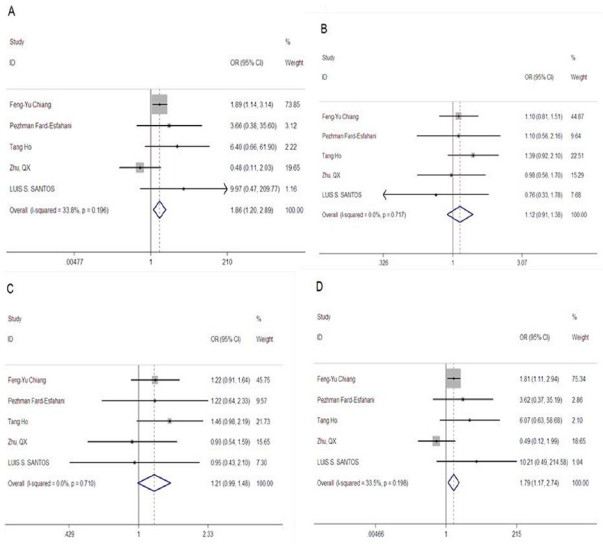

Figure 2. Forest Plots for the Association Between XRCC1 Arg194Trp Polymorphism and DTC Risk after Excluding Ri A Ryu's Study. A: Trp/Trp vs. Arg/Arg. B: Arg/Trp vs. Arg/Arg. C:Trp/ Trp +Arg/ Trp vs. Arg/Arg. D:Trp / Trp vs. Arg/ Trp + Arg/Arg

at a time. The potential publication bias was investigated with a funnel plot. In addition, Egger's linear regression (Egger et al., 1997) was used to quantitatively analyze the potential publication bias. All statistical tests were two-sided and the significance level was set at $P < 0.05$.

Results

Study selection and characteristics of studies

This meta-analysis conformed to the PRISMA statement (D Moher et al., 2009). Figure 1 illustrates the study selection process and the detailed characteristics of the included studies are shown in Table 1. A total of 10 published studies (1,606 DTC patients and 3,577 controls) were included in the Arg399Gln analysis (Zhu et al., 2004; Siraj et al., 2008; Chiang et al., 2008; Ho et al., 2009; Akulevich et al., 2009; Sigurdson et al., 2009; Ryu et al., 2011; Garcia-Quispes et al., 2011; Fard-Esfahani et al., 2011; Santos et al., 2012), 3 of which involved Asian populations (Zhu et al., 2004; Chiang et al., 2008; Ryu et al., 2011), and 6 were of Caucasian populations (Siraj et al., 2008; Sigurdson et al., 2009; Akulevich et al., 2009; Fard-Esfahani et al., 2011; Garcia-Quispes et al., 2011; Santos et al., 2012). The genotypic distribution of the controls was consistent with HWE, with the exception of two studies (Sigurdson et al., 2009; Ryu et al., 2011). Six relevant studies with a total number of 1,015 cases and 1,581 controls were included in the Arg194Trp analysis (Zhu et al., 2004; Chiang et al., 2008; Ho et al., 2009; Fard-Esfahani et al., 2011; Ryu et al., 2011; Santos et al., 2012). Three of these included Asian populations (Zhu et al., 2004; Chiang et al., 2008; Ryu et al., 2011), and two included a Caucasian population (Fard-Esfahani et al., 2011; Santos et al., 2012). Six relevant studies with a total number of 1,284 cases and 2,265 controls were included in the Arg280His analysis (Siraj et al., 2008; Chiang et al., 2008; Ho et al., 2009; Akulevich et al., 2009; Fard-Esfahani et al., 2011; Garcia-Quispes et al., 2011); one of these was based on Asian populations (Chiang et al., 2008), and four on Caucasian populations (Siraj et al., 2008; Akulevich et al., 2009; Fard-Esfahani et al., 2011; Garcia-Quispes et al.,2011).

Meta-analysis results

The main findings of the meta-analysis and heterogeneity test are shown in Table 2. No significant association was observed between Arg399Gln polymorphism and risk of DTC in all genetic models of the overall meta-analysis (Table 2 and Figure 2). Moreover, in the subgroup analysis, there was no evidence of significant association between Arg399Gln polymorphism and risk of DTC (Table 2). However, a significant association was found between the Trp/Trp vs Arg/Arg, recessive model and DTC susceptibility after excluding one study in the Arg194Trp meta-analysis (Ryu et al., 2011), because it showed a significant effect of gender between cases and controls even though the higher incidence of DTC among women than men is already well-known (Parkin et al., 2005), the corresponding ORs and 95%CIs were 1.87 (1.20–2.90) and 1.79 (1.17–2.74), respectively (Table 2). As well, the significant association was also found in the dominant model of Arg280His polymorphism and DTC susceptibility in Caucasian (Table 2).

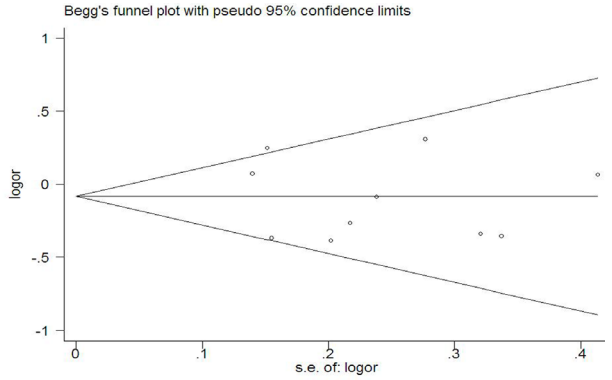

Figure 3. Funnel Plot of XRCC1 Arg399Gln Polymorphism and Risk of DTC for Publication bias in Dominant Model

Tests of heterogeneity

We found heterogeneities in some meta-analyses of the three polymorphisms (in which $I^2 > 50\%$), therefore random-effects models were implemented to produce the corresponding results; otherwise the fixed-effects models were applied (Table 2).

Sensitivity analysis

Sensitivity analysis was performed to assess the influence of each study on the pooled OR by omitting individual studies one at a time. The results suggested that no individual study significantly affected the pooled ORs in our meta-analysis.

Publication bias

Funnel plots and Egger's tests were performed to evaluate publication bias. The shape of the funnel plots revealed no evidence of obvious asymmetry in the dominant model (Figure 3). Egger's regression tests suggested an absence of publication bias in the meta-analysis of the three polymorphisms (Table 2).

Discussion

Until now, association studies have identified a variety of predisposing variants for DTC, demonstrating a high level of genetic heterogeneity for this tumor (Bonora et al., 2010). In the present study, we examined the relationship between three nsSNPs of the XRCC1 gene and risk of DTC. Qian et al., also conducted a similar study of this topic (Yi et al., 2012), however they extracted the wrong number (in fact, the GLN/GLN of Arg399Gln polymorphism in the control group was 20 (Fard-Esfahani et al., 2011), while the corresponding number was 11 in their article). After careful examination, we found that the fixed effects model was used to calculate the result of the ethnicity analysis (Asian) in Arg399Gln polymorphism in Table 2 in their study, however due to the $I^2 > 50\%$, they should apply the random effects model, thus the right result should be [1.56 (0.63-3.86) for the aa vs AA, $I^2=63.1\%$; 1.50 (0.64-3.51) for the recessive model, $I^2=59.2\%$]. Besides, the number of Asian study and Caucasian studies in Arg194Trp meta-analysis were both 3 in table 1 in their meta-analysis, however in the sub-group analysis stratified by ethnicity in table 2, the number of study included in Asian and Caucasian meta-analysis were 4 and 2 respectively, there is no way that they can do the meta-analysis with less 3 studies. Furthermore, the authors demonstrated that they already tested the Hardy–Weinberg equilibrium in the control populations, however the control populations of the Arg399Gln polymorphism in Ryu's (Ryu et al., 2011) and Sigurdson's (Sigurdson et al., 2009) study were not in accordance with Hardy-Weinberg equilibrium. The figure 2 in their article was wrong, because the horizontal axis and vertical axis should represent the logOR and s.e.of:logOR instead of OR and s.e.of:OR. Obviously, the authors are not familiar the meta-analysis, and are irresponsible for these many mistakes. Of note, we included one more study in our meta-analysis (Santos et al., 2012). All in all, they extracted the wrong number, calculated wrongfully, and the conclusions of the Arg399Gln polymorphism were based on a few studies, therefore their meta-analysis may not be reliable and believable, most important of all, the results of their study are not replicated.

Our results suggest a significant association between the Arg194Trp polymorphism and DTC risk, which is consistent with the findings of Chiang et al. (2008). We excluded one study from the Arg194Trp meta-analysis (Ryu et al., 2011), because it showed a significant effect of gender between cases and controls even though the higher incidence of DTC among women than men is already well-known (Parkin et al., 2005). Once this was excluded, the results of the Arg194Trp meta-analysis were more stable and reliable. However, as the number of studies included in this meta-analysis was small, the results should be interpreted with particular caution.

To date, the epidemiological studies of the association between Arg399Gln and DTC susceptibility have yielded conflicting results. The study reported by Zhu et al. revealed a significant correlation between the XRCC1 Arg399Gln polymorphism and DTC risk in a codominant model (4.65, 1.24–17.4) (Zhu et al., 2004), while, by contrast, Tang et al. found the same polymorphism to be a protective factor for DTC (Ho et al., 2009). Similarly contradictory data existed for the Arg280His polymorphism (Fard-Esfahani et al., 2011), while we evidenced a significant association between the dominant model of Arg280His polymorphism and DTC susceptibility in Caucasian. These differences may reflect variations environmental factors, sample size and unknown confounding factors. As the allele frequencies of control populations differed when classified according to ethnicity, this may also be caused by variations in ethnic background.

To explore all possible heterogeneities, we performed a sub-group analysis according to the control sources (hospital versus population-based controls), as hospital-based controls might not be fully representative of the general population. Indeed, we found obvious heterogeneities in hospital-based studies, which may explain our meta-analysis heterogeneity. When such heterogeneity is present, the results of this study should be interpreted with particular caution.

The advantages of our meta-analysis are the following. It was more reliable than any single study, and that no publication bias was observed in the funnel plots and Egger's tests. To explore the heterogeneity, we excluded

two studies that were not consistent with HWE (Ryu et al., 2011; Sigurdson et al., 2009), and performed sub-group analysis according to ethnicity and source of control. However, our study has some limitations. First, the studies eligible for meta-analysis were relatively small in number. Second, our meta-analysis did not include haplotype analysis. The combination of the three genotypes may be more discriminating as a risk factor than a single locus genotype. Third, our literature search was mainly restricted to papers published in the English language, so it is possible that studies in other languages were systematically excluded. Finally, not all of the included studies adjusted for potential confounders (the articles included in our meta-analysis didn't provide the detailed genotype information on age, gender, and smoking in their data), which might have influenced the results of our study.

In conclusion, this meta-analysis demonstrated that the XRCC1 Arg194Trp polymorphism might be a risk factor for DTC. Further well designed studies involving larger sample sizes and considering more confounding factors such as gender, life style, and environmental factors are now needed to fully elucidate the role of the three XRCC1polymorphisms in DTC susceptibility. In addition, as DTC is believed to be induced by both environmental and host factors, gene-environment and gene-gene interactions should also be examined.

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