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TNF-α −308 G/A variant and susceptibility to chronic obstructive pulmonary disease: A systematic review and meta-analysis

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ABSTRACT

Background and objective: TNF-α −308 G/A variant is recognized to play an important role in the pathogenesis of chronic obstructive pulmonary disease (COPD). Although many studies have investigated the association of TNF-α−308 and COPD risk, a deep understanding of this association is lacking due to small subjects sizes and insufficiently study designs among different investigations. In this study, a systematic review and meta-analysis was performed based on published reports on the association of TNF-α and COPD.

Method: The published studies concerned the association between TNF-α and COPD were identified using a systematic research in Scopus, Google Scholar, and PubMed up to April 2018. A total of 46 different papers studying the rs1800629 variant in TNF-α gene were included. Then, human studies were selected to further analysis regardless of papers language.

Results: Based on the results, the major outcome of this meta-analysis can be represented as follows: individuals with GG and GA genotypes possess less risk of developing COPD (OR = 0.58, 95%CI: (0.44–0.79), P < 0.00) compared to AA genotype carriers. In contrast, the AA genotype carriers of the TNF-α rs1800629 has a significantly higher risk of developing COPD (OR = 1.83, 95%CI: (1.34–2.51), P < 0.00) compared to GG carrier. Despite the previous meta-analysis results which reported significantly decreasing of heterogeneity with ethnicity, we found that the source of controls has a significant contribution to observed heterogeneity.

Conclusions: Thanks to the global burden of COPD studies, proving TNF-α 308 gene variant as an independent factor in its pathogenesis opens new insights to diagnosis and management of COPD.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease associated with chronic inflammatory responses in lungs and airways. According to WHO, COPD is now the fourth cause of death worldwide, and it is predicted to become the third global cause of death by 2020 [1]. Tobacco use is the main risk factor for COPD as 80–90% of COPD cases have a history of smoking [2,3]. Although the definite pathophysiological mechanism of COPD has not been characterized yet, the critical role of both environmental and genetic factors in COPD as a complex polygenic disease has frequently been demonstrated. To date, many genetic association studies have been conducted for COPD to identify as much as 500 variants genes associated with the disease, most of which are involved in oxidative stress and inflammation pathways, especially Tumor necrosis factor-alpha (TNF-α). TNF-α is a pleiotropic inflammatory cytokine that functions in many inflammatory conditions, including growth inhibition and promotion, inflammation, angiogenesis, cytotoxicity, and immunomodulation [4]. A large number of studies supports the pathobiologic role of TNF-α in COPD development and its increase in the circulation, bronchial biopsies, and bronchoalveolar lavage fluid of COPD patients [5], as TNF-α inhibitors (such as etanercept, golimumab, and infliximab) have been considered as new potential medications in COPD [6]. TNF-α protein is regulated through the TNF-α gene promoter that is affected, to a great extent, by the TNF-α −308 single nucleotide polymorphism (SNP) (rs1800629; the G-A transition) located at its proximity. Allele A carriers show a higher production of TNF-α than allele G carriers. Although some meta-analyses have been conducted to clarify the association between TNF-α and risk of COPD, most of them belonged to before 2016 [7], and many studies have been performed since then. Therefore, the present study

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tried to re-evaluate the associations between TNF-α and COPD development through an updated meta-analysis up to April 2018.

2. Materials and methods

2.1. Search strategy

Published papers concerned the association between TNF-α and COPD were identified using a systematic research in Scopus, Google Scholar, and PubMed up to April 2018. The keywords were as follows: [TNF-α OR Tumor Necrosis Factor-α OR Tumor necrosis factor alpha] **AND** [chronic obstructive pulmonary disease OR COPD] **AND** [variant OR mutation OR gene polymorphism]. The investigation on human cases was selected to further analysis regardless of papers language. More articles not included in the searched databases were explored through the cross-check of references after reviewing articles based on inclusion criteria.

2.2. Inclusion and exclusion criteria

The following items were considered for inclusion criteria: (1) Sufficient genotype frequency data in case and control groups; (2) Case-control designs; (3) TNF-α and COPD association studies; and (4) smokers or healthy individuals as control groups. Meta-analysis articles and reviews were excluded. Studies evaluating simultaneously another pathologic state beside COPD, animal studies, or violated Hardy-Weinberg equilibrium were excluded. In addition, variants reported in two or fewer reports were not included.

2.3. Data extraction and quality assessment

Based on inclusion and exclusion criteria, the data were collected by two independent reviewers. Disagreements were discussed and solved within a team group. Each study was categorized and recorded based on the following characteristics: the author's name, year of publication, country and ethnicity of participants, studied SNP, genotyping technique, control and genotype distributions, and number of cases.

2.4. Statistical analysis

The metafor (version 1.9–4) package of R (version 3.1.1) was employed to perform all statistical tests. The deviation of genotype distributions in the control groups of each study from Hardy-Weinberg equilibrium was evaluated using the Chi-square test. Five different genetic models were used to perform the meta-analysis for each SNPs, including Recessive, Additive, Allele contrast, Dominant and co-dominant models.

P value < 0.05 was considered to show a statistically significant difference. Z-test was applied to extracted data in order to indicate the statistical significance of odds ratio (OR) with the corresponding 95% confidence intervals (CIs). Cochran's Q-statistic (significance at $P_Q < 0.10$) was used to address between-study heterogeneity which quantified by I^2 metrics. In cases with heterogeneity, the data was collected by the random-effects model (fitted by restricted maximum-likelihood estimator), and for other cases, the fixed-effects model was employed. Potential sources of heterogeneity were explored using multivariate meta-regressions. The sources could be found among the following moderators: sample size, control sources (smokers or healthy individuals), and ethnicity (Caucasian, Asian, and others). Sources and ethnicity of controls were utilized to carry out sub-group analyses. To evaluate the stability of acquired P-values, a leave-one-out sensitivity analysis was conducted. Egger regression asymmetry test and funnel plot were used to consider publication bias. A *t*-test was also performed to determine the significance of the intercept. The p-value < 0.1 was considered for statistically significant publication bias.

Fig. 1. Flow diagram of the search process.

3. Results

3.1. Study description and characteristics

Among 628 papers reviewed, only 46 articles met the inclusion criteria. The major finding of the articles was summarized in table-S1. One variant across the TNF-α gene (−308 G/A) was considered in the meta-analysis. The Search process flow chart was shown in Fig. 1.

3.2. Quantitative data synthesis

3.2.1. TNF-α −308 variant and COPD susceptibility

5402 cases and 7247 controls were reported in 46 studies evaluating the association of TNF-α −308 (rs1800629) G/A variants and COPD (Supplementary file, Table-S1). The significant association between COPD and TNF-α −308 variant was proved under Recessive model (OR = 0.58, 95% CI: 0.44–0.79, P < 0.00), Dominant model (OR = 1.65, 95% CI: 1.36–2.01, P < 0.00), co-dominant model (OR = 1.53, 95% CI: (1.27–1.83), P < 0.00), and Additive model (OR = 1.83, 95% CI: 1.34–2.51, P < 0.00), but not under Allele contrast model (OR = 1.39, 95% CI: 0.98–1.97, $P = 0.06$) (Table 1 & Supplementary file, Fig. S1). Sub-group analysis based on the resources and ethnicity of controls revealed that, under the allele contrast model, the significant association was only observed in Asians. However, under additive, dominant, recessive, and Co-dominant models this association remained significant in healthy controls and Asians.

3.2.2. Heterogeneity analysis

The significant evidence was found for between-studies heterogeneity (P < 0.1 and $I^2 > 50\%$). Allele contrast, Dominant, and Co-dominant models (Table 1) were found to be dominant for TNF-α −308 (rs1800629) G/A heterogeneity. Meta-regression was conducted to clarify potential sources of between-study heterogeneity (Table 2). It was noticed that the source of controls has significant contributions to the observed heterogeneity (P < 0.001). The significance of residual Cochran's test ofheterogeneity was proved (Q_E p < 0.01). The significance level in this paper was set under 0.01.

Table 1
Meta-analysis of TNF-α rs1800629 variant association with COPD risk.

Genetic model	Test for association			Test for heterogeneity		
	OR (95%CI)	Z	*P*	Q	*P*	I^2 (%)
Allele contrast (A vs. G)	1.39 (0.98–1.97)	1.86	0.06	771.47	< 0.00	93.19
Additive (AA vs. GG)	1.83 (1.34–2.51)	3.78	< 0.00	51.36	0.38	9.23
Dominant (AA + AG vs. GG)	1.65 (1.36–2.01)	5.06	< 0.00	157.27	< 0.00	71.59
Recessive (GG + GA vs. AA)	0.58 (0.44–0.79)	−3.61	< 0.00	43.51	0.69	0.00
Co-dominant (AG vs. AA + GG)	1.53 (1.27–1.83)	4.55	< 0.00	128.44	< 0.00	64.92

Table 2
Meta-regression results for between-study heterogeneity assessment using the study sample size, source of controls and ethnicity as confounding variables.

Genetic model	Residual heterogeneity		Test of moderators	
	Q_E	P	Q_M	p
Allele contrast (G vs. A)	765.60	< 0.00	3.84	0.69
Dominant (AA + AG vs. GG)	140.36	< 0.00	31.86	< 0.00
Co-dominant (AG vs. AA + GG)	70.12	0.00	2.05	0.02

3.2.3. Sensitivity analysis

The leave-one-out sensitivity analysis was performed by iteratively removing one study at a time to confirm stability of the findings. Table 3 and supplementary files as well as Tables S2–S5 represent the results. It was demonstrated that excluding the Gong et al. [8], Stankovic et al. [9], Shukla et al. [10], Ozdogan et al. [11], Tarigan et al. [12], Reséndiz-hernández et al. [13], and Rodriguez et al. [14] studies from the analysis could result in different *P* values for the association of TNF-α −308 (rs1800629) and COPD risk, under allele contrast model (Table 3). The significance levels did not obviously change under other models (Supplementary files, Tables S2–S5).

3.2.4. Publication bias

Egger's test and funnel plot were used to examine publication bias under all genetic comparisons for TNF-α −308 (rs1800629) G/A variant (Table 4 & Supplementary file, Fig. S2). Combining all studies together, we found no clear asymmetry under all genetic models.

4. Discussion

In vivo and *in vitro* studies have shown that the increased production of TNF-α could result in a pro-oxidative response, late-phase airway inflammation, and hyperresponsiveness, indicating that oxidant/antioxidant imbalance has a major role in the pathogenesis of COPD [51–53]. The increased level of TNF-α in COPD patients can result from gene variations events that may induce up-regulating TNF-α expression [14]. Case-control studies reported inconsistent results between the TNF-α level and COPD risk, as some found positive associations and some did not, possibly due to factors including ethnicity, sources of controls, sample size, and gene-environmental interactions. These inconsistencies were also reported in the Brogger et al meta-analysis demonstrating no association for both overall and subgroup analyses [22], possibly due to the limited number of studies they included. In another meta-analysis, Gingo demonstrated a positive association between the TNF-α level and COPD risk [15], although their meta-analysis included only 16 studies and ethnicity did not stratify the analysis. This association among Asians had been also shown significantly in previous meta-analyses [54–56], though the same association was not reported in Caucasians. In line with these findings, we found a significant association in Asians according to the case of additive, dominant, recessive, and co-dominant model. Moreover, the smoking status effect on the association between the TNF-α−308A allele and risk of COPD was addressed only in Zhang meta-analysis [57]. In a recent meta-analysis, Zhang et al [7] suggested that the A allele of TNF-α −308 is a risk factor for developing COPD. They found that individuals with GA genotype are less susceptible than AA genotypes to develop

Table 3
Sensitivity analysis of the association between TNF-α rs1800629 and COPD risk, under the allele contrast model.

Author	OR (95%CI)	Z value	P	Q	Qp	I^2
Gingo [15]	1.38(0.97–1.97)	1.79	0.07	768.90	0.00	93.25
Hsieh [16]	1.39(0.97–1.98)	1.81	0.07	771.08	0.00	93.38
Zhang [17]	1.37(0.96–1.96)	1.76	0.08	766.47	0.00	93.30
Du [18]	1.38(0.97–1.96)	1.77	0.08	767.23	0.00	93.29
Gong [8]	1.45(1.02–2.04)	2.08	0.04	759.73	0.00	93.09
Shi [19]	1.38(0.97–1.96)	1.77	0.08	765.08	0.00	93.24
Zhang [20]	1.38(0.97–1.96)	1.77	0.08	769.23	0.00	93.36
Zhang [20]	1.38(0.97–1.97)	1.80	0.07	770.92	0.00	93.39
Papatheodorou [21]	1.41(0.99–2.01)	1.91	0.06	768.30	0.00	93.27
Brogger [22]	1.4(0.98–2)	1.87	0.06	769.13	0.00	92.95
Broekhuizen [23]	1.4(0.98–2)	1.85	0.06	771.32	0.00	93.17
Seifart [24]	1.4(0.98–1.99)	1.85	0.07	771.46	0.00	93.21
Chierakul [25]	1.39(0.98–1.98)	1.83	0.07	771.36	0.00	93.38
Hegab [26]	1.38(0.97–1.96)	1.81	0.07	771.02	0.00	93.35
Ma [27]	1.37(0.96–1.95)	1.75	0.08	768.70	0.00	93.34
Jiang [28]	1.4(0.98–1.99)	1.86	0.06	771.43	0.00	93.40
Jiang [28]	1.38(0.97–1.97)	1.79	0.07	770.62	0.00	93.39
Zui (2004)	1.37(0.97–1.96)	1.76	0.08	768.40	0.00	93.35
Ma [29]	1.37(0.96–1.94)	1.73	0.08	766.70	0.00	93.32
Ferrarotti [30]	1.41(0.99–2)	1.88	0.06	770.87	0.00	93.37
He [31]	1.38(0.97–1.97)	1.79	0.07	770.30	0.00	93.38
Kucukaycan [32]	1.4(0.98–2)	1.87	0.06	770.20	0.00	93.08
Sakao [33]	1.38(0.97–1.96)	1.77	0.08	765.03	0.00	93.23
Higham [34]	1.41(0.99–2.01)	1.88	0.06	769.60	0.00	93.22
Keatings [35]	1.4(0.98–2)	1.85	0.06	771.31	0.00	93.23
Huang [36]	1.35(0.95–1.92)	1.69	0.09	758.26	0.00	93.21
Ishii [37]	1.39(0.98–1.98)	1.85	0.06	771.48	0.00	93.37
Shi [38]	1.37(0.96–1.96)	1.76	0.08	767.15	0.00	93.32
Li [39]	1.37(0.96–1.96)	1.76	0.08	766.70	0.00	93.31
Jiang [40]	1.36(0.96–1.94)	1.72	0.09	761.72	0.00	93.26
Li [41]	1.37(0.96–1.95)	1.75	0.08	762.19	0.00	93.23
Tang [42]	1.37(0.96–1.95)	1.74	0.08	765.75	0.00	93.31
Zhang [17]	1.37(0.96–1.96)	1.76	0.08	766.47	0.00	93.30
Stankovic [9]	1.42(1–2.02)	1.95	0.05	764.26	0.00	93.23
Trajkov [43]	1.4(0.98–2)	1.86	0.06	771.34	0.00	93.31
Chen [44]	1.41(0.99–2.01)	1.90	0.06	768.86	0.00	93.26
Yao [45]	1.38(0.97–1.97)	1.78	0.08	764.22	0.00	93.12
Shukla [10]	1.42(1–2.02)	1.95	0.05	761.23	0.00	93.16
Wang [46]	1.37(0.96–1.95)	1.74	0.08	765.56	0.00	93.31
Yang [47]	1.37(0.96–1.95)	1.74	0.08	766.09	0.00	93.31
Ozdogan [11]	1.42(0.99–2.02)	1.93	0.05	768.76	0.00	93.32
Chiang [48]	1.37(0.96–1.94)	1.74	0.08	767.89	0.00	93.33
Wu [49]	1.37(0.96–1.96)	1.75	0.08	763.27	0.00	93.25
Hsieh [16]	1.39(0.97–1.98)	1.82	0.07	771.25	0.00	93.40
Rodriguez [14]	1.42(1–2.02)	1.97	0.05	769.55	0.00	93.30
Tarigan [12]	1.42(1–2.02)	1.93	0.05	765.20	0.00	93.22
Reséndiz-Hernández [13]	1.38(0.97–1.97)	1.78	0.07	768.83	0.00	93.31
Reséndiz-Hernández [13]	1.6(1.33–1.92)	5.00	0.00	165.87	0.00	73.14
Reséndiz-Hernández [50]	1.38(0.97–1.97)	1.77	0.08	765.23	0.00	93.20
Reséndiz-Hernández [50]	1.38(0.97–1.97)	1.79	0.07	770.76	0.00	93.39

Table 4
Egger test result for the TNF-α rs1800629 variant association with COPD risk.

Genetic model	Test for asymmetry	
	t	P
Allele contrast (A vs. G)	0.90	0.36
Additive (AA vs. GG)	0.67	0.50
Dominant (AA + AG vs. GG)	1.61	0.11
Recessive (GG + GA vs. AA)	−0.45	0.65
Co-dominant (AG vs. AA + GG)	1.14	0.25

COPD. These results were supported by the subgroup analysis in Asians. In addition, Zhang L et al. found that there is no association between the TNF-α −308 G/A variant and the risk of COPD in smokers and non-smokers [7], but Zhang et al. demonstrated a relation between TNF-α −308 G/A variant and COPD risk in smokers [57].

In this meta-analysis, the authors tried to review and update the association between TNF-α −308 (rs1800629) and COPD risk. Based on our results, the major outcome are as follows: individuals with GG and GA genotypes possess a lower risk of developing COPD (OR = 0.58, 95%CI: (0.44–0.79), P < 0.00) compared to AA genotype carriers. In contrast, AA genotype carriers of TNF-α −308 rs1800629 have a significantly higher risk of developing COPD (OR = 1.83, 95%CI: (1.34–2.51), P < 0.00) compared to GG carriers. Despite previous meta-analyses reporting a significant decrease in heterogeneity with ethnicity [7,54,56,57], we found that the source of controls has a significant contribution to observed heterogeneity. Furthermore, there was no publication bias in the present meta-analysis indicating the reliability of results.

5. Conclusions

There is a significant relationship between the TNFa − 308A genotype and increased risk of COPD. GA genotype individuals were observed to be less susceptible to developing COPD compared to the AA genotype. Thanks to the global burden of COPD, proving TNFa − 308 gene variant as an independent factor involved in the pathogenesis of COPD opens new insights to diagnosis and management of the disease.

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Declaration of Competing Interest

No conflict of interest.

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Appendix A. Supplementary material

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