GMR Genetics and Molecular Research
Online Journal
ISSN:1676-5680

Dual role of vitamin D-binding protein 1F allele in chronic obstructive pulmonary disease susceptibility: a meta-analysis

M. Xiao[1,2], T. Wang[1], T. Zhu[1] and F. Wen[1,2]

[1]Division of Pulmonary Diseases, State Key Laboratory of Biotherapy of China, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, Sichuan, China
[2]Department of Respiratory Medicine, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, Sichuan, China

Corresponding author: F. Wen
E-mail: respmed@163.com

Genet. Mol. Res. 14 (2): 3534-3540 (2015)
Received May 14, 2014
Accepted October 27, 2014
Published April 17, 2015
DOI http://dx.doi.org/10.4238/2015.April.17.1

ABSTRACT. Vitamin D-binding protein (DBP), a highly polymorphic serum protein, encoded by GC gene, is important in the development of chronic obstructive pulmonary disease (COPD). This meta-analysis was performed to assess the association between GC polymorphisms (1F, 1S, and 2 alleles) and COPD susceptibility. Published case-control studies were retrieved from the Pubmed, Embase, and China National Knowledge Infrastructure databases. After data extraction, pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Seven case-control studies were included. Pooled effect size showed that GC polymorphisms were not significantly associated with COPD susceptibility. According to ethnicity, the 1F allele was significantly correlated with COPD susceptibility in Asians (1F *vs* 1S, OR: 1.52, 95%CI: 1.16-2.00 and 1F *vs* 2, OR: 1.87, 95%CI: 1.42-2.44), indicating that individuals with the 1F allele have an increased risk of COPD compared to those with the 1S or 2 allele. However, the 1F allele was

associated with a lower, insignificant risk of COPD than the 1S and 2 alleles in Caucasians (1F *vs* 1S, OR: 0.83, 95%CI: 0.64-1.08 and 1F *vs* 2, OR: 0.73, 95%CI: 0.54-0.98). Moreover, no significant association was found for the 1S and 2 alleles in Asians (OR: 1.23, 95%CI: 0.90-1.69) and Caucasians (OR: 0.89, 95%CI: 0.70-1.13). After excluding each study, the pooled results were robust and no publication bias was observed. We found that the GC 1F allele confers a risk of COPD in Asians, whereas the 1F allele may protect against COPD in Caucasians.

Key words: Chronic obstructive pulmonary disease; Polymorphism; Vitamin D-binding protein

INTRODUCTION

Vitamin D-binding protein (DBP), also known as GC globulin, a glycosylated α-globulin protein with high circulation levels, serves as the major plasma carrier protein of vitamin D and its metabolites. In addition to its specific binding capacity, DBP exerts several other important biological functions, such as actin scavenging, fatty acid transport, macrophage activation, and chemotaxis, through its 3 distinct domains (Dimeloe and Hawrylowicz, 2011; Wood et al., 2011).

DBP is a highly polymorphic serum protein, encoded by GC gene that is located on chromosome 4 in human with 3 common alleles (1F, 1S, and 2). Horne et al. (1990) first reported that GC gene polymorphisms are associated with chronic bronchitis and emphysema in Caucasians. Associations between GC gene polymorphisms and chronic obstructive pulmonary disorder (COPD) have been established over the past decade (Ishii et al., 2001; Laufs et al., 2004; Ito et al., 2004; Lu et al., 2004; Korytina et al., 2006; Shen et al., 2010). However, the GC gene was not identified as a candidate gene for COPD in recent genome-wide association studies (GWAS) (Artigas et al., 2012). This may be because most recent GWAS were performed in Northern European populations (Todd et al., 2011) and single-nucleotide polymorphisms may have been significant but did not reach a genome-wide level of significance (Haq et al., 2010). Thus, it remains unclear whether GC polymorphisms are associated with COPD risk.

Differences in ethnicity and sample size in individual studies may explain the inconsistent results with low statistical power, and a meta-analysis may be useful for pooling the independent statistical powers and thus achieving a quantitative understanding regarding the associations. In the present study, we conducted a meta-analysis to determine the association between GC polymorphisms and COPD risk.

MATERIAL AND METHODS

Search strategy

A literature search was conducted using Pubmed, Embase, and China National Knowledge Infrastructure (http://www.cnki.net/) databases. The following search terms were utilized: Vitamin D-binding protein or GC globulin, and gene or polymorphism or variant, and chronic obstructive pulmonary disease or COPD.

Data extraction

Two independent reviewers collected the data based on inclusion and exclusion criteria. For inclusion in the meta-analysis, retrieved articles had to include the number of cases and controls, as well as the number of individual genotypes in cases and controls. Exclusion criteria in the meta-analysis were: 1) not a case-control genetic study, 2) duplicated report, and 3) no useful data reported. Unpublished data were not considered. Disagreement was resolved by discussion before reaching a consensus. If more than 1 article was published by the same group using the same cases, the study with the higher sample size was selected.

Statistical analyses

Categorical variables were presented as the odds ratio (OR) with the 95% confidence interval (CI). Pooled ORs with 95%CIs were calculated and $P < 0.05$ was considered to be statistically significant. Heterogeneity was evaluated using the Q test. Meta-analysis was conducted using the fixed-effects model when there was no heterogeneity ($P \geq 0.1$); otherwise, the random-effects model was used. Subgroup analysis was performed by ethnicity to assess the effect of possible clinical heterogeneity on the summary ORs. Each study was subjected to sensitivity analysis to confirm the consistency of the overall effect size. Funnel plots, as well as the Begg rank correlation test and Egger linear regression test, were used to determine potential publication bias, and $P < 0.05$ was considered to be significant publication bias. All analyses were conducted using Revman 5.0 (Oxford, UK) and Stata 11.0 (StataCorp LP, College Station, TX, USA).

RESULTS

Studies included in the meta-analysis

Fifteen articles were relevant to the search terms. After reviewing the titles, abstracts, and articles, 9 articles were excluded and 6 articles with 7 case-control studies matched the inclusion criteria (Figure 1). Of the 6 studies included, 4 were published in English, 1 was published in Chinese, and 1 was published in Russian. These studies were carried out in China, Japan, Russia, and Iceland. Notably, the study by Korytina et al. (2006) was performed in 2 ethnic populations (Tatar and Russia). The main features of the studies included in this meta-analysis are presented in Table 1.

Quantitative synthesis

Pooled effect size showed no significant association between GC polymorphisms and COPD risk (Figures 2-4). In the subgroup analysis by ethnicity, the 1F allele was significantly correlated with COPD susceptibility in Asians. However, the 1F allele had a lower, but not significant risk for COPD compared to the 1S and 2 alleles in Caucasians. Moreover, when comparing the 1S and 2 alleles, no significant association was found in Asians and Caucasians. The main results of pooled estimates in the meta-analysis are presented in Table 2.

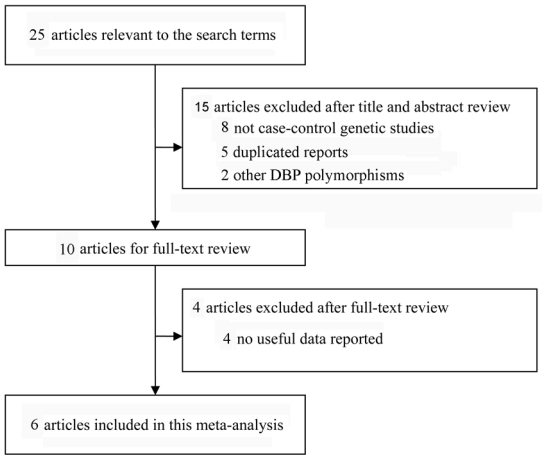

Figure 1. Flow diagram of search process.

Table 1. Main characteristics of included studies.

Ref	Country	Ethnicity	Source of control	Genotyping	Genotype							Allele		
					Total	1F-1F	1F-1S	1F-2	1S-1S	1S-2	2-2	1F	1S	2
Ishii et al., 2001	Japan	Asian	Healthy population	PCR + RFLP	63[a]	23	15	16	1	6	2	77	23	26
					82[b]	17	27	18	5	8	7	79	45	40
Laufs et al., 2004	Iceland	Caucasian	Healthy population	PCR + RFLP	102[a]	1	11	5	39	35	11	18	124	57
					183[b]	2	24	8	68	67	14	36	227	95
Ito et al., 2004	Japan	Asian	Healthy smoker	PCR + RFLP	103[a]	33	29	25	3	11	2	120	46	40
					88[b]	15	27	30	5	10	1	87	47	42
Lu et al., 2004	China	Asian	Healthy smoker	PCR + RFLP	69[a]	23	15	16	5	9	1	77	34	27
					52[b]	6	16	14	3	8	5	42	30	32
Korytina et al., 2006	Russia	Caucasian	Healthy population	PCR + RFLP	131[a]	8	26	25	30	29	13	67	115	80
					106[b]	12	39	9	14	25	7	72	92	48
Korytina et al., 2006	Russia	Caucasian	Healthy population	PCR + RFLP	166[a]	14	31	20	42	49	10	79	164	89
					130[b]	14	29	12	25	45	5	69	124	67
Shen et al., 2010	China	Asian	Healthy population	PCR + RFLP	100[a]	35	20	22	7	13	3	112	47	41
					100[b]	13	26	29	4	12	16	81	46	73

PCR = polymerase chain reaction; Ref = reference; RFLP = restriction fragment length polymorphism; [a]COPD, chronic obstructive pulmonary disease; [b]Control.

Test of heterogeneity

Significant overall heterogeneity was observed between all studies for 1F *vs* 1S (I^2 = 47%, P = 0.08) and 1F *vs* 2 (I^2 = 77%, P = 0.0002), but not 1S *vs* 2 comparisons. The source of heterogeneity was detected based on ethnicity. When stratified by ethnicity, no heterogeneity was observed, suggesting that the heterogeneity between studies in Asians and Caucasians contributed to the overall heterogeneity in 1F *vs* 1S and 1F *vs* 2 comparisons.

Sensitivity analyses

After exclusion of each study, the pattern of the pooled effect size was significant in the 1F *vs* 1S and 1F *vs* 2 comparisons according to the ethnicity, indicating the stability of the results.

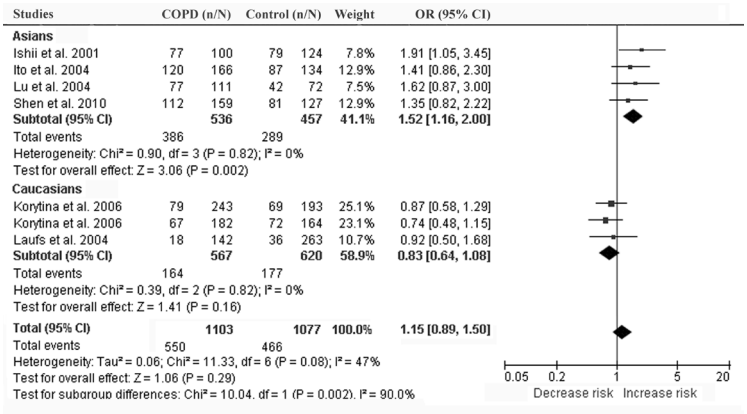

Figure 2. Forest plots of OR with 95%CI for the association between GC polymorphisms and COPD risk subanalyzed by ethnicity in 1F *vs* 1S.

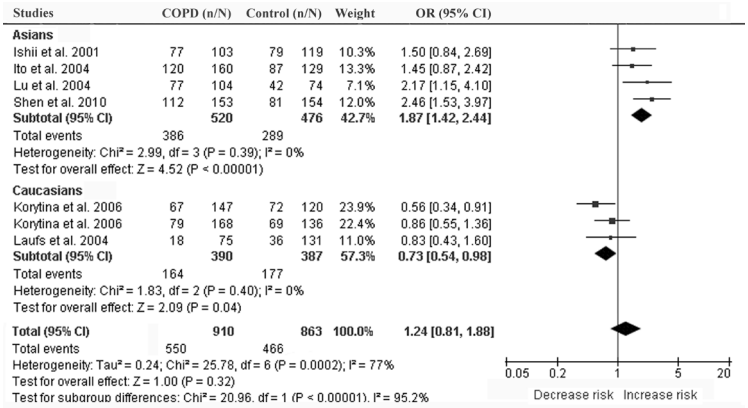

Figure 3. Forest plots of OR with 95%CI for the association between GC polymorphisms and COPD risk subanalyzed by ethnicity in 1F *vs* 2.

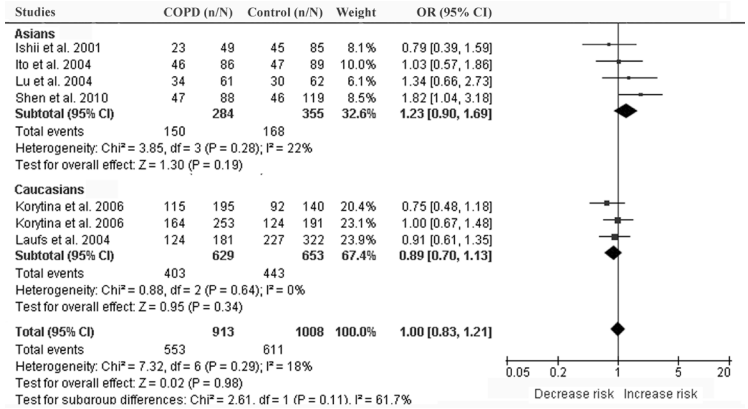

Figure 4. Forest plots of OR with 95%CI for the association between GC polymorphisms and COPD risk subanalyzed by ethnicity in 1S *vs* 2.

Table 2. Main results of pooled estimates in the meta-analysis.

Groups	Effect Size [OR (95%CI); P value; statistic model]		
	1F *vs* 1S	1F *vs* 2	1S *vs* 2
Overall	1.15 (0.89-1.50); 0.29; Random	1.24 (0.81-1.88); 0.32; Random	1.00 (0.83-1.21); 0.98; Fixed
Asians	1.52 (1.16-2.00); 0.002; Fixed	1.87 (1.42-2.44); <0.0001; Fixed	1.23 (0.90-1.69); 0.19; Fixed
Caucasians	0.83 (0.64-1.08); 0.16; Fixed	0.73 (0.54-0.98); 0.04; Fixed	0.89 (0.70-1.13); 0.34; Fixed

Publication bias

The funnel plots showed no significant asymmetry in this meta-analysis (Figure 5). Moreover, publication bias was not detected using Begg's rank correlation test (1F *vs* 1S: P = 1.000, 1F *vs* 2: P = 0.764, 1S *vs* 2: P = 0.764) and Egger's linear regression test (1F *vs* 1S: P = 0.942, 1F *vs* 2: P = 0.557, 1S *vs* 2: P = 0.403).

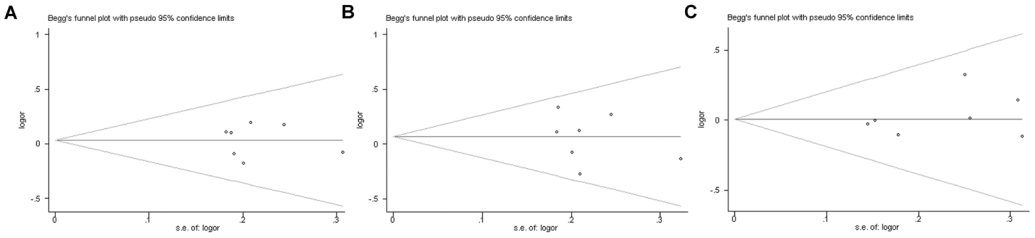

Figure 5. Begg's funnel plot for evaluation of publication bias in the included studies for the association between GC polymorphisms and COPD risk (**A.** 1F *vs* 1S; **B.** 1F *vs* 2; **C.** 1S *vs* 2).

DISCUSSION

DBP, a highly polymorphic serum protein, contributes to the development of COPD. Over the past decade, the association between GC polymorphisms and COPD risk has been increasingly examined because of its potential important biological functions in COPD pathogenesis.

In this meta-analysis, no significant association between GC polymorphisms and COPD risk was found. Moreover, significant overall heterogeneity was revealed between all studies in the 1F *vs* 1S and 1F *vs* 2 comparisons. To identify the source of heterogeneity, subgroup analysis was performed according to ethnicity. No heterogeneity was observed between studies in Asians and Caucasians. Further, the results indicated that the 1F allele was significantly correlated with COPD susceptibility in Asians, suggesting that individuals with the 1F allele are at an increased risk of COPD compared with those with the 1S or 2 allele. However, the 1F allele confers a lower, but not significant risk for COPD compared to the 1S and 2 alleles in Caucasians. However, Laufs et al. (2004) reported that the 1F allele is associated with sputum hypersecretion in a Caucasian population at an increased risk for COPD. The limited sample size (48 cases) may explain the different results, and based on the present meta-analysis, the 1F allele may be a protective factor for COPD in Caucasians, although this should be validated in additional studies. Moreover, after exclusion of each study, the pattern of the pooled effect size persisted, and publication bias was not suggested in the present study, possibly because of the search strategy and data extraction methods used.

There were some limitations to this study. First, there have been few large sample size studies, leading to low pooled statistical power. Second, the pooled estimates were not adjusted by confounding factors such as gender, age, and smoking history. Third, lack of the original data in the studies limited our further analysis of the potential interactions between genes or genes and the environment, which may modulate COPD risk.

In conclusion, although the pooled estimates should be interpreted with caution, our meta-analysis suggests that the GC 1F allele is a risk factor for COPD in Asians, whereas the 1F allele may have a protective role for COPD in Caucasians. However, large sample size studies using unbiased genotyping methods, standardized defined COPD cases, and matched controls in different populations, as well as more detailed data regarding the interaction between individuals and the environment, are warranted.

Conflicts of interest

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

Research supported by the Applied Basic Research Projects of Sichuan Province (#2013JY0032).

REFERENCES

Artigas MS, Wain LV and Tobin MD (2012). Genome-wide association studies in lung disease. *Thorax* 67: 271-273.

Dimeloe S and Hawrylowicz C (2011). A direct role for vitamin D-binding protein in the pathogenesis of COPD? *Thorax* 66: 189-190.

Haq I, Chappell S, Johnson SR, Lotya J, et al. (2010). Association of MMP -12 polymorphisms with severe and very severe COPD: a case control study of MMPs -1, 9 and 12 in an European population. *BMC Med. Genet*. 11: 7.

Horne SL, Cockcroft DW and Dosman JA (1990). Possible protective effect against chronic obstructive airways disease by the GC2 allele. *Hum. Hered*. 40: 173-176.

Ishii T, Keicho N, Teramoto S, Azuma A, et al. (2001). Association of Gc-globulin variation with susceptibility to COPD and diffuse panbronchiolitis. *Eur. Respir. J*. 18:753-757.

Ito I, Nagai S, Hoshino Y, Muro S, et al. (2004). Risk and severity of COPD is associated with the group-specific component of serum globulin 1F allele. *Chest* 125: 63-70.

Korytina GF, Akhmadishina LZ, Ianbaeva DG and Viktorova TV (2006). Genotypes of vitamin-D-binding protein (DBP) in patients with chronic obstructive pulmonary disease and healthy population of Republic Bashkortostan. *Mol. Biol.* 40: 231-238.

Laufs J, Andrason H, Sigvaldason A, Halapi E, et al. (2004). Association of vitamin D binding protein variants with chronic mucus hypersecretion in Iceland. *Am. J. Pharmacogenomics* 4: 63-68.

Lu M, Yang B and Cai Y (2004). The relationship between vitamin D binding protein gene polymorphism and chronic obstructive pulmonary disease. *Zhong Hua Nei Ke Za Zhi* 43: 117-120.

Shen LH, Zhang XM, Su DJ, Yao SP, et al. (2010). Association of vitamin D binding protein variants with susceptibility to chronic obstructive pulmonary disease. *J. Int. Med. Res*. 38: 1093-1098.

Todd JL, Goldstein DB, Ge D, Christie J, et al. (2011). The state of genome-wide association studies in pulmonary disease: a new perspective. *Am. J. Respir. Crit. Care Med*. 184: 873-880.

Wood AM, Bassford C, Webster D, Newby P, et al. (2011). Vitamin D-binding protein contributes to COPD by activation of alveolar macrophages. *Thorax* 66: 205-210.