CC16 Gene A38G Polymorphism and Susceptibility to Asthma: An Updated Meta-analysis

Dan Cheng¹,², Honghong Di¹,², Zheng Xue³ and Guohua Zhen¹,²

Abstract

Objective  To comprehensively evaluate the association between the CC16 gene A38G polymorphism and the risk of asthma.

Methods  Studies were retrieved from databases including PubMed, EMBASE, Web of Science and the Chinese Biomedical Literature Database according to the inclusive and exclusive criteria. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of the associations.

Materials  Fifteen case-control studies with 1,623 cases and 3,294 controls were recruited for the analysis of the association between the CC16 gene A38G polymorphism and the risk of asthma.

Results  The overall ORs showed no significant associations between the CC16 gene A38G polymorphism and the risk of asthma (AA vs. GG: OR=1.04, 95%CI=0.86-1.25; AG vs. GG: OR=1.08, 95%CI=0.94-1.24; AA + AG vs. GG: OR=1.07, 95%CI=0.94-1.22; AA vs. AG + GG: OR=1.01, 95%CI=0.85-1.19; A vs. G: OR=1.04, 95%CI=0.95-1.14). Moreover, similar results were obtained in the subgroup analysis stratified by ethnicity (Asian: AG vs. GG: OR=1.02, 95%CI=0.87-1.21; Caucasian: AG vs. GG: OR=1.22, 95%CI=0.94-1.57) and age (Child: AG vs. GG: OR=1.21, 95%CI=0.84-1.74; Adult: AG vs. GG: OR=1.06, 95%CI=0.91-1.23).

Conclusion  CC16 gene A38G polymorphism is not associated with the risk of asthma.

Key words: CC16, single nucleotide polymorphism, asthma, meta-analysis

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Introduction

Asthma is one of the most common chronic inflammatory respiratory diseases (1). The hallmarks of asthma include allergic airway inflammation, bronchial hyper-responsiveness, mucus hyperplasia and airway remodeling (2). It has been shown that asthma is a complex disease that results from interactions between environment and genetic factors (3-5). The associations between the risk of asthma and gene polymorphisms, such as single nucleotide polymorphism (SNPs), have been studied extensively. Recently, a number of studies have investigated the association between the risk of asthma and the CC16 gene A38G polymorphism (6-15).

CC16, also known as homo sapiens secretoglobin, family 1A, member 1 (SCGB1A1), Clara cell 10 kDa protein (CC10) or Clara cell secretory protein (CCSP) (16-18), is secreted by non-mucous, non-ciliated airway epithelial cells (19, 20). CC16 is the main component of the extracellular lining fluid of airways (21). It has been shown that CC16 plays an important role in the inhibition of airway inflammation and the pathogenesis of asthma (19, 22). Compared with wild-type mice, CC16-deficient mice exhibit significantly higher levels of Th2 cytokines with pulmonary eosinophilia after antigen sensitization and challenges (23). In addition, Van Vyve reported that the levels of CC16 proteins are reduced in the bronchoalveolar lavage fluid in asthmatic patients (24). Moreover, the CC16 protein expression is downregulated in the small airways and reduced in the serum in asthmatic subjects (25-28).
The human CC16 gene is located on chromosome 11q13 (29). The A38G polymorphism (dbSNP rs3741240) is an adenine/guanine polymorphism located 38 bp downstream from the transcription start site of the CC16 gene (30, 31). The A38G polymorphism is a major genetic determinant of the serum CC16 level and has been identified to be a potential susceptibility factor for the development and severity of asthma (6, 12, 30). The A allele is also associated with reduced gene transcription, with 25% lower transcription levels than the G allele (29, 32, 33). Thus far, a number of studies have reported an association between the CC16 gene A38G polymorphism and the risk of asthma (6-8, 10, 12). However, this association was not replicated in several other studies (9, 11, 13).

Because single studies with a small sample size may have low power to draw reliable conclusions, we performed a meta-analysis including 15 case-control studies in order to assess the relationship between the CC16 gene A38G polymorphism and asthma susceptibility.

**Data source**

We performed a literature search using the electronic databases PubMed, EMBASE, Web of Science and the Chinese Biomedical Literature Database (CBM) to identify articles that evaluated the association between the CC16 gene A38G polymorphism and asthma susceptibility. The search terms were as follows: (“asthma” or “asthmatic”) and (“polymorphism” or “mutation” or “variant”) and (“CC16” or “CC10” or “CCSP” or “SCGB1A1”) and (“polymorphism” or “mutation” or “variant”). The literature search was last updated on February 28, 2014.

**Study selection**

The following criteria were used to select the studies included in this meta-analysis: (1) an evaluation of the association between the CC16 gene A38G polymorphism and asthma susceptibility; (2) a case-control study; (3) the availability of genotype distributions in both cases and controls; (4) genotype distributions in the control population consistent with Hardy-Weinberg equilibrium (HWE). The following exclusion criteria were used: (1) abstracts or reviews; (2) lack of reporting of genotype frequencies; (3) design based on family or sibling pairs. For overlapping studies, only the study with the largest sample numbers was included.

**Data extraction**

Two authors independently reviewed the full text of the included articles and extracted relevant data. The following information was collected: first author’s name, year of publication, country of origin, ethnicity, sample size, genotyping methods and number of genotype frequencies in the cases and controls. Any discrepancies between the two authors were resolved by discussion, and a third author assessed the disputed articles.

**Statistical analysis**

For each case-control study, we first examined whether the genotype distribution in the control group was consistent with HWE using Pearson’s X² test. The OR and 95% CI were calculated to assess the strength of the association between the CC16 gene A38G polymorphism and the risk of asthma. The significance of the summary ORs was determined according to the Z test, with a p value of <0.05 considered to be statistically significant. We also assessed the risk of homozygote comparison (AA vs. GG), heterozygote comparison (AG vs. GG) and dominant (AA+AG vs. GG), recessive (AA vs. AG+GG) and additive (A vs. G) genetic model comparisons.

The heterogeneity between studies was assessed using the X² test based on the Cochrane Q-test. A p value of >0.10 for the Q-test indicates lack of heterogeneity among the studies. The pooled OR estimate of each study was then calculated according to the fixed-effects model. Otherwise, the random-effects model was used. F was also calculated to test heterogeneity among the included studies, with F<25%, 25-75% and >75% considered to represent a low, moderate and high degree of heterogeneity, respectively (34). Publication bias was examined using Begg’s funnel plot and Egger’s test (35). All statistical analyses were completed using the Revman 5.1 (Nordic Cochrane Center, Copenhagen, Denmark) and STATA 10.0 (Stata Corporation, College Station, USA) software programs.

**Results**

**Characteristics of the studies**

Overall, 77 articles were recruited from the databases mentioned in the Materials and methods section. Sixty-two articles were excluded for the following reasons: 18 articles were duplications or reviews, 15 articles were not relevant to asthma, three articles were not relevant to the CC16 gene, 14 articles did not examine the A38G polymorphism in patients with the CC16 gene, eight studies were not case-control studies, three articles did not provide sufficient data and one study included subjects with allergic rhinitis as a control group. Finally, 15 case-control studies with a total of 1,623 cases and 3,294 controls met the inclusion criteria and were included in the analysis (Fig. 1).

The main characteristics of the 15 studies included in the meta-analysis are summarized in Table 1. There were eight studies of Asians and seven studies of Caucasians. Twelve studies were performed in adults, and three studies were performed in children. Healthy subjects or subjects without symptoms or a history of allergic diseases, such as asthma, allergic rhinitis or atopic dermatitis, matched for age and sex were used as controls. Polymerase chain reaction (PCR)
was performed as a genotyping method. The genotype frequencies and HWE examination results are shown in Table 2.

**Quantitative synthesis**

The association between the CC16 gene A38G polymorphism and the risk of asthma is summarized in Table 3. Overall, no significant associations were found between the CC16 gene A38G polymorphism and the risk of asthma (AA vs. GG: OR=1.04, 95%CI=0.86-1.25, p=0.72; AG vs. GG: OR=1.08, 95%CI=0.94-1.24, p=0.30; AA + AG vs. GG: OR=1.07, 95%CI=0.94-1.22, p=0.28; AA vs. AG + GG: OR=1.01, 95%CI=0.85-1.19, p=0.95; A vs. G: OR=1.04, 95%CI=0.95-1.14, p=0.43; Fig. 2).

Moreover, similar results were obtained in the stratified subgroup analysis. For example, no significant associations were observed between the CC16 gene A38G polymorphism and the risk of asthma in the subgroup analysis stratified by ethnicity (Asian: AG vs. GG: OR=1.02, 95%CI=0.87-1.21, p=0.79; AA + AG vs. GG: OR=1.02, 95%CI=0.88-1.20, p=0.77; Caucasian: AG vs. GG: OR=1.22, 95%CI=0.94-1.57, p=0.13; AA + AG vs. GG: OR=1.21, 95%CI=0.95-1.54, p=0.13; Fig. 3). Moreover, there were no significant associations in the subgroup analysis stratified by age (Child: AG vs. GG: OR=1.21, 95%CI=0.84-1.74, p=0.30; AA + AG vs. GG: OR=1.13, 95%CI=0.80-1.61, p=0.49; Adult: AG vs. GG: OR=1.06, 95%CI=0.91-1.23, p=0.48; AA + AG vs. GG: OR=1.07, 95%CI=0.92-1.23, p=0.38; Fig. 4).

**Sensitivity analysis**

In order to assess the stability of the results of the meta-analysis, we performed a sensitivity analysis by sequentially excluding each individual study. Statistically similar results were obtained after sequentially excluding each study, sug-
Table 2. Distribution of CC16 Genotype and Allele among Asthmatic Patients and Controls

| Reference Year | Case | Control | Case | Control | HWE |
|----------------|------|---------|------|---------|-----|
|                | GG   | GA      | AA   | GG      | GA  |
| 6 2003         | 35   | 43      | 6    | 57      | 49  | 12  | 113 | 55 | 163 | 73 | 0.76 |
| 6 2003         | 48   | 48      | 8    | 57      | 49  | 12  | 144 | 64 | 163 | 73 | 0.76 |
| 7 2004         | 68   | 119     | 72   | 62      | 115 | 74  | 255 | 263| 239 | 263 | 0.2 |
| 8 2004         | 45   | 31      | 9    | 58      | 23  | 4   | 121 | 49 | 139 | 31 | 0.39 |
| 9 2002         | 37   | 39      | 11   | 17      | 18  | 6   | 113 | 61 | 52  | 30 | 0.73 |
| 10 2000        | 16   | 16      | 4    | 27      | 29  | 8   | 48  | 24 | 83  | 45 | 0.96 |
| 11 1998        | 54   | 61      | 10   | 55      | 76  | 19  | 169 | 81 | 186 | 114 | 0.36 |
| 11 1998        | 36   | 15      | 19   | 36      | 50  | 14  | 121 | 79 | 122 | 78 | 0.61 |
| 12 2005        | 41   | 40      | 19   | 36      | 50  | 14  | 122 | 78 | 122 | 78 | 0.61 |
| 13 2003        | 13   | 21      | 16   | 26      | 16  | 8   | 47  | 53 | 68  | 32 | 0.06 |
| 14 2003        | 18   | 19      | 4    | 30      | 21  | 4   | 55  | 27 | 81  | 29 | 0.9 |
| 15 2013        | 54   | 67      | 20   | 206     | 273 | 103 | 175 | 107| 685 | 479 | 0.45 |
| 15 2013        | 59   | 65      | 26   | 206     | 273 | 103 | 183 | 117| 685 | 479 | 0.45 |
| 15 2013        | 65   | 111     | 37   | 206     | 273 | 103 | 241 | 185| 685 | 479 | 0.45 |

HWE: p value for Hardy-Weinberg equilibrium for CC16 gene A38G polymorphism among controls.

Table 3. Total and Stratified Analysis of the CC16 Gene A38G Polymorphism on Risk of Asthma

| Variables     | No. of Case/Control | Case vs. Control | OR(95% CI) | Case vs. Control | OR(95% CI) | Case vs. Control | OR(95% CI) | Case vs. Control | OR(95% CI) | Case vs. Control | OR(95% CI) |
|---------------|---------------------|------------------|------------|------------------|------------|------------------|------------|------------------|------------|------------------|------------|
| Total         | 12                  | 1,623/3,294      | 1.04(0.86-1.25) | p=0.72          | 1.08(0.94-1.24)| p=0.30          | 1.07(0.94-1.22)| p=0.28          | 1.01(0.85-1.19)| p=0.95          | 1.04(0.95-1.14) | p=0.43      |
| Ethnicity     |                     |                  |            |                  |            |                  |            |                  |            |                  |            |
| Asian         | 8                   | 1,098/2,332      | 1.00(0.80-1.25)| p=1.00          | 1.02(0.87-1.21)| p=0.79          | 1.02(0.88-1.20)| p=0.77          | 0.99(0.81-1.20)| p=0.90          | 1.01(0.90-1.12) | p=0.89      |
| Caucasian     | 7                   | 525/962          | 1.16(0.78-1.73)| p=0.46          | 1.22(0.94-1.57)| p=0.13          | 1.21(0.95-1.54)| p=0.13          | 1.07(0.74-1.55)| p=0.71          | 1.12(0.94-1.34) | p=0.19      |
| Age           |                     |                  |            |                  |            |                  |            |                  |            |                  |            |
| Child         | 3                   | 224/300          | 0.81(0.43-1.53)| p=0.52          | 1.21(0.84-1.74)| p=0.30          | 1.13(0.80-1.61)| p=0.49          | 0.74(0.41-1.36)| p=0.34          | 1.01(0.78-1.32) | p=0.92      |
| Adult         | 12                  | 1,399/2,994      | 1.06(0.87-1.33)| p=0.55          | 1.06(0.91-1.23)| p=0.48          | 1.07(0.92-1.23)| p=0.38          | 1.03(0.86-1.24)| p=0.72          | 1.04(0.94-1.15) | p=0.42      |

a Number of studies

Figure 2. Association between CC16 gene A38G and the risk of asthma in the overall population (GA vs. GG)

suggesting the stability of the results.

Publication bias

Begg’s funnel plot and Egger’s test were used to assess the publication bias of the included studies. No publication bias was observed in Begg’s funnel plot (Fig. 5), and there were no significant differences according to Egger’s weighted regression method (p for bias =0.230). These data indicate that there was no significant publication bias among the studies included in this meta-analysis.
Figure 3. Association between CC16 gene A38G and the risk of asthma in the subgroup analysis stratified by ethnicity (GA vs. GG).

| Subgroup | Asthma Events | Control Events | Total Events | Weight | Odds Ratio M.H. Fixed, 95% CI |
|----------|--------------|----------------|--------------|--------|--------------------------------|
| 2.1.1 Asian | 1-3 Sharma S2004 | 119 | 187 | 115 | 177 | 11.2% | 0.94 [0.81, 1.14] |
| 1-4 Saadat M 2004 | 31 | 76 | 23 | 91 | 3.4% | 1.74 [0.99, 3.39] |
| 1-7 Gao P (alcoholic)1998 | 10 | 81 | 50 | 86 | 6.4% | 0.70 [0.38, 1.29] |
| 1-7 Gao P (inhaled)1998 | 21 | 34 | 16 | 42 | 1.4% | 2.63 [1.03, 6.68] |
| 11 Gu G 2003 | 17 | 41 | 18 | 45 | 1.4% | 2.71 [1.02, 7.16] |
| 13 Taniguchi N(Early)2013 | 67 | 121 | 273 | 479 | 12.8% | 0.94 [0.83, 1.04] |
| 13 Taniguchi N(Late)2013 | 65 | 124 | 273 | 479 | 13.9% | 0.63 [0.56, 1.24] |
| Subtotal (95% CI) | 111 | 176 | 273 | 479 | 14.1% | 1.29 [0.90, 1.84] |

Total events: 515
Heterogeneity: CH² = 11.58, df = 7 (P = 0.12); I² = 49%
Test for overall effect: Z = 0.27 (P = 0.79)

Figure 4. Association between CC16 gene A38G and the risk of asthma in the subgroup analysis stratified by age (GA vs. GG).

| Subgroup | Asthma Events | Control Events | Total Events | Weight | Odds Ratio M.H. Fixed, 95% CI |
|----------|--------------|----------------|--------------|--------|--------------------------------|
| 2.1.1 Child | 1-3 Sharma S2004 | 43 | 78 | 49 | 106 | 4.9% | 1.43 [0.79, 2.57] |
| 1-4 Saadat M 2004 | 48 | 96 | 49 | 106 | 6.1% | 1.06 [0.57, 2.02] |
| 1-5 Mansur AH 2002 | 10 | 36 | 18 | 35 | 3.1% | 1.00 [0.45, 2.22] |
| 1-6 Laing IA 2000 | 18 | 32 | 29 | 56 | 2.9% | 0.93 [0.39, 2.22] |
| 1-7 Gao P (British)1998 | 49 | 85 | 50 | 86 | 5.5% | 0.69 [0.53, 1.80] |
| 10 Candelaria PV 2005 | 25 | 38 | 20 | 37 | 3.3% | 0.61 [0.22, 1.56] |
| 12 Kalyoncu AF 2003 | 19 | 37 | 21 | 51 | 2.2% | 1.51 [0.84, 2.74] |
| Subtotal (95% CI) | 1356 | 2768 | 1000% | 1.08 [0.94, 1.24] |

Total events: 754
Heterogeneity: CH² = 2.39, df = 6 (P = 0.88); I² = 0%
Test for overall effect: Z = 1.51 (P = 0.13)
Test for subgroup differences: Not available

| Subgroup | Asthma Events | Control Events | Total Events | Weight | Odds Ratio M.H. Fixed, 95% CI |
|----------|--------------|----------------|--------------|--------|--------------------------------|
| 2.1.2 Adult | 1-3 Sharma S2004 | 119 | 187 | 115 | 177 | 11.2% | 0.94 [0.81, 1.14] |
| 1-4 Saadat M 2004 | 31 | 76 | 23 | 91 | 3.4% | 1.74 [0.99, 3.39] |
| 1-7 Gao P (alcoholic)1998 | 88 | 156 | 85 | 131 | 8.7% | 0.92 [0.49, 1.85] |
| 1-7 Gao P (inhaled)1998 | 10 | 50 | 50 | 86 | 6.4% | 0.70 [0.38, 1.29] |
| 10 Candelaria PV 2005 | 25 | 38 | 20 | 37 | 3.3% | 0.60 [0.22, 1.56] |
| 12 Kalyoncu AF 2003 | 19 | 37 | 21 | 51 | 2.2% | 1.51 [0.84, 2.74] |
| Subtotal (95% CI) | 111 | 176 | 273 | 479 | 14.1% | 1.29 [0.90, 1.84] |

Total events: 847
Heterogeneity: CH² = 14.07, df = 11 (P = 0.23); I² = 22%
Test for overall effect: Z = 0.71 (P = 0.48)

Total events: 754
Heterogeneity: CH² = 15.23, df = 14 (P = 0.38); I² = 8%
Test for overall effect: Z = 1.05 (P = 0.30)
Test for subgroup differences: Not available
Discussion

*CC16* plays an important role in the inhibition of airway inflammation and pathogenesis of asthma (19, 22). The A38G polymorphism is a major genetic determinant of the serum *CC16* level and has been identified to be a potential susceptibility factor for the development and severity of asthma. A number of original studies have reported an association between the *CC16* gene A38G polymorphism and the risk of asthma with inconclusive results, possibly due to the small sample size and relatively low statistical power of these studies. In order to better understand this association, we conducted a meta-analysis including 1,623 cases and 3,294 controls from 15 published case-control studies assessing the association between the *CC16* gene A38G polymorphism and asthma.

The results of our meta-analysis indicated that the *CC16* gene A38G polymorphism is not associated with an increased risk of asthma in the overall population. We obtained the same results in the subgroup analysis stratified by ethnicity and age. Several factors may account for the lack of contribution of the *CC16* gene A38G polymorphism to the risk of asthma. Asthma is a genetically complex disease caused by multiple genetic and environmental factors, and gene-gene and gene-environment interactions may have an effect on the development of the asthma phenotype. For example, exposure to environmental challenges, such as cigarette smoking and air pollution, which cause oxidative stress and an inflammatory response, may interact with the anti-inflammatory function of the *CC16* gene. Therefore, studies with more a stringent design considering environmental factors, such as cigarette smoking, are required to validate the findings of this meta-analysis.

Heterogeneity among the studies included in meta-analyses will affect the final conclusion. Moderate heterogeneity was observed under most of the genetic models in this meta-analysis. The degree of heterogeneity can be attributed to the limited number of included studies and differences in ethnic and genetic backgrounds, environmental exposure or methodological factors in design between these studies. As the publication of findings often depends on the expectations of the researchers, false-positive results may be magnified or false-negative results may be suppressed (36). In the present meta-analysis, Begg’s funnel plot and Egger’s test showed that there was no significant publication bias among the included studies.

This meta-analysis is associated with several limitations. First, the number of included studies and subjects in the overall population and subgroup analyses were relatively small. Second, all included studies were published in English or Chinese indexed by the selected databases. Therefore, studies published in other languages may have been missed. Third, subgroup analyses according to age at asthma onset or the presence of atopic versus non-atopic asthma, although important, could not be performed in this meta-analysis because such data were not available in the included studies. In spite of these limitations, the present meta-analysis has some advantages. First, the quality of the case-control studies included in this meta-analysis was good and met the inclusion criteria. Second, we did not detect any obvious publication bias, indicating that the whole pooled results were unbiased.

In summary, the present meta-analysis showed that there is no association between the *CC16* gene A38G polymorphism and an increased risk of asthma in the overall population. In order to validate the findings of this meta-analysis, additional large scale case-control studies with a more strin-
gent design considering environmental factors, such as cigarette smoking, and detailed information regarding age at onset and the atopic status are required.

The authors state that they have no Conflict of Interest (COI).

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