Asthma susceptible genes in Chinese population: A meta-analysis

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Abstract

Background: Published data regarding the associations between genetic variants and asthma risk in Chinese population were inconclusive. The aim of this study was to investigate asthma susceptible genes in Chinese population.

Methods: The authors conducted 18 meta-analyses for 18 polymorphisms in 13 genes from eighty-two publications.

Results: Seven polymorphisms were found being associated with risk of asthma, namely: A Disintegrin and Metalloprotease 33 (ADAM33) T1-C/T (odds ratio [OR] = 6.07, 95% confidence interval [CI]: 2.69-13.73), Angiotensin-Converting Enzyme (ACE) D/I (OR = 3.85, 95%CI: 2.49-5.94), High-affinity IgE receptor β chain (FcεRI) -6843G/A (OR = 1.49, 95%CI: 1.01-2.22), Interleukin 13(IL-13) -1923C/T (OR = 2.99, 95%CI: 2.12-4.24), IL-13 -2044A/G (OR = 1.49, 95%CI: 1.07-2.08), Regulated upon Activation, Normal T cell Expressed and Secreted (RANTES) -28C/G (OR = 1.64, 95% CI: 1.09-2.46), Tumor Necrosis Factor-α (TNF-α) -308G/A (OR = 1.42, 95%CI: 1.09, 1.85). After subgroup analysis by age, the ACE D/I, β2-Adrenergic Receptor (β2-AR) -79G/C, TNF-α -308G/A, Interleukin 4 receptor(IL-4R) -1902G/A and IL-13 -1923C/T polymorphisms were found significantly associated with asthma risk in Chinese children. In addition, the ACE D/I, FcεRIβ -6843G/A, TNF-α -308G/A, IL-13 -1923C/T and IL-13 -2044A/G polymorphisms were associated with asthma risk in Chinese adults.

Conclusion: ADAM33, FcεRIβ, RANTES, TNF-α, ACE, β2-AR, IL-4R and IL-13 genes could be proposed as asthma susceptible genes in Chinese population. Given the limited number of studies, more data are required to validate these associations.

Introduction

Asthma is one of the most common chronic respiratory diseases, affecting about 300 millions of children and adults worldwide[1]. In China, more than 25 millions people are asthmatic patients, which includes almost 10 million children[2]. Compared with the western world, the preventive controls and treatments for asthma were not well established in China [3]. Only a few percent of asthma patients received proper treatment. Poverty and inadequate resources are the main hindrance to reduce the burden of disease in China especially in numerous of Chinese villagers. Therefore, the best approach to reduce asthma is primary prevention through modifying the risk factors of asthma.

It is well accepted that asthma is a complex disease and both genetic and environmental factors contribute to its inception and evolution[4,5]. Many studies regarding associations between genetic variants and asthma risk have been published and many genes were proposed as asthma susceptible genes[6-9]. However, the conclusions obtained from different populations were often different or even controversial. Possible roles may be that different genetic backgrounds and environment exposures in different ethnic population that may affect the pathogenesis of asthma. Thus, asthma susceptible genes in different population may not be the same.

In recent years, host genetic susceptibility to asthma has been a research focus in scientific community in China. Many genes were suggested as asthma risk
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Factors for Chinese population; however, many of the studies drew incompatible or even contradictory results. Considering a small number of sample size may be lack of power to reveal the reliable conclusion, we carried out a meta-analysis to assess the susceptible genes for asthma in Chinese population. To our knowledge, this is the first comprehensive and largest genetic meta-analysis conducted in people of Chinese descent for any respiratory diseases.

Materials and methods

Literature search
We conducted a literature search by using the electronic database Medline (Ovid), Pubmed, Embase, ScienceDirect, Springer, CNKI, Wanfang database, Weipu database and CBM database to identify articles that evaluated the association between genetic variants and the risk of asthma in Chinese population (Last search was updated on May 13, 2010). The search terms were used as follows: ‘asthma or asthmatic’, in combination with ‘polymorphism or variant or mutation’ and ‘Chinese or China’ for Medline (Ovid), Pubmed, Embase, ScienceDirect, Springer database; ‘asthma or asthmatic’, in combination with ‘polymorphism or variant or mutation’ for CNKI database, Wanfang database, Weipu database and CBM database. All languages were included. The following criteria were used for selecting literatures in the meta-analysis: (1) the study should evaluate the association between genetic variants and risk of asthma in Chinese population from either mainland, overseas or both, (2) the study should be a case-control design published in a journal (3) genotype distributions in both cases and controls were available for estimating an odds ratio with 95% confidence interval (CI) and P value, (4) genotype distributions of control population must be consistent with Hardy-Weinberg equilibrium (HWE), P > 0.05 (5) the polymorphism for data synthesis should be studied in at least three case-control studies, (6) polymorphisms for data synthesis should be characterized as -A/B, with the following genotypes: AA, AB and BB. Accordingly, the following exclusion criteria were used: (1) abstracts and reviews, (2) genotype frequency not reported, (3) repeated or overlapping publications (4) polymorphisms with data less than three case-control studies (5) genotype distributions of control population not consistent with HWE, (6) genetic variants not characterized as -A/B. For duplication or overlapping publications, the studies with larger number of cases and controls or been published latest were included.

Data extraction
Two independent authors (Xiaobo Li and Yonggang Zhang) checked all potentially relevant studies and reached a consensus on all items. In case of disagreement, a third author (Jie Zhang) would assess these articles. The following data were collected from each study: first author, year of publication, location of the people, ages, genotype frequencies in cases and controls.

Statistical Analysis
For each case-control study, we first examined whether the genotype distribution in control group was according to Hardy-Weinberg equilibrium by Pearson’s $X^2$ test http://ihg2.ensembl-euro惮enchen.de/cgi-bin/hw/hwa1.pl.

Any polymorphism that had been studied in at least three case-control studies was included in the meta-analysis. The strength of the associations between asthma risk and genetic variants were estimated by ORs and 95% CIs. The statistical significance of summary ORs were assessed by Z-test. The evaluated genetic models for each study were based mostly on those used in primary studies. Heterogeneity was evaluated by a $X^2$-based Q statistic and was considered statistical significant at $P$ value < 0.10. $I^2$ was used to measure the percentage of variability in point estimated that due to heterogeneity rather than sampling error. When the $P$-value is > 0.10, the pooled OR was calculated by the fixed-effects model, otherwise, a random-effects model was used. To evaluate the age-specific effects, subgroup analyses were performed by age for polymorphisms which were investigated in a sufficient number of studies (data were available from at least three case-control studies for at least one subgroup). Publication bias was examined by using the funnel plots, Begg’s test and Egger’s test[4]. The funnel plot is asymmetrical when there is evidence of publication bias. All statistical tests were performed by using REVMAN 4.2 software and STATA 10.0.

Results

Candidate asthma-genes in Chinese Population
The selection process is shown in Figure 1. Briefly, 2489 search results were identified from Medline (Ovid), Pubmed, Embase, ScienceDirect, Springer, CNKI database, Wanfang database, Weipu database and CBM database in the initial search. After reading the titles and abstracts, 2159 articles were excluded for abstracts, reviews, duplicated search results or not being relevant to genetic variants and asthma risk in Chinese population. By reading through the full texts of the remaining 330 articles, 7 articles were excluded for not being relevant to polymorphisms and asthma risk. The remaining 323 articles were used for data extraction. A total of 539 case-control studies were extracted from 248 articles, and 75 articles were excluded because of the absence of the usable data or not a case-control design. In meta-analysis, a small number of studies weaken the conclusions; therefore, only polymorphisms which had been investigated in at least three case-control studies were included.
for data synthesis. Thus, we excluded all these polymorphisms which were studied in less than three case-control studies. A total of 260 case-control studies were excluded. Hence, a total of 279 case-control studies were left. In addition, genotype frequencies for control population in 53 case-control studies were not consistent with HWE and these case-control studies were all excluded. In the remaining 226 case-control studies, data in 45 case-control studies were overlapped or duplicated with other studies and these case-control studies were all excluded. Thus, 181 case-control studies were left. Among the 181 case-control studies, some polymorphisms were studied in less than three case-control studies, and these polymorphisms were also excluded (a total of 62 case-control studies were excluded). Finally, a total of 18 polymorphisms in 13 genes in 119 case-control studies concerning genetic variants and asthma risk in Chinese population met the inclusion criteria, were identified for data synthesis (Table 1). The characteristics of each polymorphism are listed in Table 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 and 19. The genetic models for pooling data are also listed in Table 1.

**Summary results of Meta-analyses**

For each polymorphism, heterogeneity was analyzed by a $X^2$-based Q statistic and was considered statistically significant at $P$-value < 0.10. When the $P$-value is less than 0.10, the pooled OR of each meta-analysis was calculated by the fixed-effects model; otherwise, a random-effects model was used. The chosen models to synthesize the data for each polymorphism can be seen in Table 20.

Forest plots of each polymorphism can be seen in Figure 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 and 19. In summary, we abstained significant results for seven polymorphisms: ADAM33 T1-C/T (OR = 6.07, 95% CI: 2.69-13.73, $Z = 4.33, P < 0.0001$), ACE D/I (OR = 3.85, ...
### Table 1 Genes identified from individual studies

| Gene   | Chromosome location of gene | Polymorphism | Aminoacid change | Genetic model | Genotypes Evaluated | Other genotypes | Cases | Controls |
|--------|----------------------------|--------------|------------------|---------------|---------------------|-----------------|-------|----------|
| β2-AR  | 5q31-32                    | -46G/A       | Arg16Gly         | Recessive     | GG                  | GA+AA           | 1796  | 1589     |
|        |                            | -79G/C       | Gln27Glu         | Recessive     | GG                  | GC+CC           | 823   | 692      |
| IL-4R  | 16p11.2-12.1               | -1902G/A     | Q576R            | Dominant      | GG+GA              | AA              | 2308  | 1971     |
|        |                            | -223G/A      | Ile/Val          | Recessive     | GG                  | GA+AA           | 1623  | 1304     |
| IL-4   | 5q31                       | -589C/T      |                  | Dominant      | CC+CT              | TT              | 1724  | 1656     |
|        |                            | -79G/C       |                  | Dominant      | GG+GA              | AA              | 1434  | 1276     |
|        |                            | -109C/T      |                  | Recessive     | CC+CT              | TT              | 342   | 371      |
| ACE    | 17q23                      | D/I          |                  | Recessive     | DD+II              |                 | 385   | 335      |
| IL-13  | 5q31                       | -2044A/G     | Gln130Arg        | Dominant      | AA+AG              | GG              | 1512  | 1351     |
|        |                            | -1923C/T     |                  | Recessive     | TT+TC              | CC+CT           | 645   | 588      |
| IL-1β  | 2q12-21                    | -511C/T      |                  | Dominant      | TT+TC              | CC              | 333   | 255      |
| LT-α   | 6q21.3                     | +252A/G      |                  | Dominant      | GG+GA              | AA              | 674   | 896      |
| TGF-β  | 1q13                       | -509C/T      |                  | Dominant      | TT+TC              | CC              | 406   | 390      |
| CD14   | 5q31.1                     | -159C/T      |                  | Dominant      | TT+TC              | CC              | 1381  | 1219     |
| ADAM33 | 20p13                      | -159C/T      |                  | Dominant      | GG+GC              |                 | 314   | 229      |
| RANTES | 17q11.2-12                 | -28G/C       |                  | Dominant      | GG+GC              |                 |       |          |

### Table 2 Main data of all studies included in the meta-analysis for the -46G/A (Arg16Gly) polymorphism in β2-AR gene

| Study             | Population location | Year | Age      | Case | Control |
|-------------------|---------------------|------|----------|------|---------|
| Chan, I H [16]    | Hong Kong           | 2008 | 10.4 ± 3.7 | 101  | 135     |
| Cui, LY(Han) [17] | Neimenggu           | 2007 | 21-62    | 6    | 34      |
| Cui, LY(Meng) [17]| Neimenggu           | 2007 | 26-69    | 3    | 21      |
| Gao, J M [18]     | Beijing             | 2004 | 38.7 ± 13.8 | 32  | 6       |
| Li, H [19]        | Shanghai            | 2009 | 3-12     | 86   | 76      |
| Liao, W [20]      | Chongqing           | 2001 | 5.8 ± 4.3 | 12   | 27      |
| Qiu, Y Y(2008) [21]| Jiangsu            | 2008 | 63.2 ± 5.6 | 25  | 31      |
| Shi, X H [22]     | Jiangsu             | 2008 | 34(14-66) | 22  | 19      |
| Wang, Z [23]      | Anhui               | 2001 | 30.6 ± 16.2 | 52  | 54      |
| Xie, Y [24]       | Shanghai            | 2008 | 49.8 ± 2.78 | 14  | 37      |
| Xing, J [25]      | Beijing             | 2001 | 20-66    | 9    | 62      |
| Zhang, X Y [26]   | Chongqing           | 2008 | 1.08-17 | 81   | 111     |
| Wang, J Y [27]    | Taiwan              | 2009 | 7.82 ± 3.81 | 138 | 207     |

### Table 3 Main data of all studies included in the meta-analysis for the -79G/C (Gln27Glu) polymorphism in β2-AR gene

| Study             | Population location | Year | Age      | Case | Control |
|-------------------|---------------------|------|----------|------|---------|
| Cui, LY(Han) [17] | Neimenggu           | 2007 | 21-62    | 32   | 6       |
| Gao, G K [28]     | Beijing             | 2002 | 4-56     | 20   | 32      |
| Liao, W [20]      | Chongqing           | 2001 | 5.8 ± 4.3 | 26  | 20      |
| Lin, Y C [29]     | Taiwan              | 2003 | 13.9 ± 0.07 | 65  | 15      |
| Pan, Y P [30]     | Jiangxi             | 2005 | -        | 15   | 24      |
| Qiu, Y Y(2000) [31]| Jiangsu            | 2000 | 42 ± 5   | 23   | 30      |
| Qiu, Y Y(2008) [21]| Jiangsu            | 2008 | 63.2 ± 5.6 | 56  | 13      |
| Wang, Z [23]      | Anhui               | 2001 | 30.6 ± 16.2 | 108 | 19      |
| Ye, X W [32]      | Guizhou             | 2003 | 42.68 ± 10.55 | 25 | 39      |
| Zhang, X Y [26]   | Chongqing           | 2008 | 1.08-17 | 54   | 119     |
95%CI: 2.49-5.94, Z = 6.07, P < 0.00001), FcεRIb-6843G/A (OR = 1.49, 95%CI: 1.01-2.22, Z = 1.99, P = 0.05), IL-13-1902G/A (OR = 1.64, 95%CI: 1.04-2.58, Z = 2.34, P = 0.02), RANTES-28C/G (OR = 1.09-2.46, Z = 2.36, P = 0.02), TNF-α -308G/A (OR = 1.42, 95%CI: 1.09-1.85, Z = 2.63, P = 0.009). These results indicated that these polymorphisms were significant associated with asthma risk in Chinese population. All results for all 18 meta-analyses are summarized in table 20.

To evaluate the age-specific effects, subgroup analyses were performed by age for polymorphisms which were investigated in a sufficient number of studies (data were available from at least three case-control studies for at least one subgroup). Three subgroups were used: adults, children, others (ages in these case-control studies were not mentioned or mixed with adults and children). Briefly, we obtained significant results from five polymorphisms (ACE D/I, β2-AR -79G/C, TNF-α -308G/A, IL-4R -1902G/A and IL-13 -1923C/T) in children and

| Table 4 Main data of all studies included in the meta-analysis for the -1902G/A (Q576R) polymorphism in IL-4R gene |
| Study | Population location | Year | Age | Case | Control |
|-------|---------------------|------|-----|------|---------|
|       |                     |      |     | AA   | AG      | GG   | AA  | AG  | GG  | OR     | 95%CI     |
| Cui, T P[33] | Hubei              | 2003 | 3-68 | 129  | 89      | 23   | 130 | 41  | 4    | 2.51    | 1.64-3.83 |
| Deng, R Q[34] | Guangdong          | 2006 | 8-75 | 26   | 42      | 32   | 15  | 38  | 47   | 0.50    | 0.25-1.02 |
| Gui, Q[35] | Chongqing          | 2006 | 49(28-72) | 33 | 15      | 2    | 34  | 4   | 2    | 1.09    | 0.48-2.52 |
| Hu, S Y[36] | Guangdong          | 2005 | 2-16 | 90   | 66      | 19   | 130 | 41  | 4    | 2.73    | 1.74-4.28 |
| Liu, L N[37] | Henan              | 2005 | 3-15 | 46   | 27      | 3    | 47  | 12  | 1    | 2.36    | 1.09-5.08 |
| Mak, J C[38] | Hong Kong          | 2007 | 42.4 ± 16.1 | 200 | 81      | 4    | 191 | 91  | 9    | 0.81    | 0.57-1.15 |
| Sun, J[39] | Heilongjiang       | 2010 | 3-14 | 67   | 24      | 0    | 33  | 9   | 0    | 1.31    | 0.55-3.14 |
| Wu, X H[40] | Hubei              | 2010 | 8.8  | 183  | 61      | 8    | 168 | 55  | 4    | 1.07    | 0.72-1.61 |
| Zhang, A M[41] | Hunan             | 2005 | 3-14 | 55   | 39      | 0    | 57  | 11  | 0    | 3.67    | 1.71-7.89 |
| Zhang, H[42] | Shanghai           | 2007 | -    | 257  | 87      | 8    | 87  | 27  | 0    | 1.19    | 0.73-1.95 |
| Zhang, W[43] | Singapore          | 2007 | -    | 115  | 30      | 0    | 115 | 38  | 4    | 0.71    | 0.42-1.22 |
| Wang, J Y[27] | Taiwan            | 2009 | 7.82 ± 3.81 | 326 | 112     | 9    | 360 | 140 | 12   | 0.88    | 0.66-1.17 |

| Table 5 Main data of all studies included in the meta-analysis for the -223G/A (Ile/Val) polymorphism in IL-4R gene |
| Study | Population location | Year | Age | Case | Control |
|-------|---------------------|------|-----|------|---------|
|       |                     |      |     | AA   | AG      | GG   | AA  | AG  | GG  | OR     | 95%CI     |
| Chan, I H[16] | Hong Kong       | 2008 | 10.4 ± 3.7 | 79   | 159     | 57   | 49  | 80  | 38   | 0.81    | 0.51-1.29 |
| Deng, R Q[44] | Guangdong        | 2006 | 8-75 | 24   | 47      | 29   | 9   | 33  | 58   | 0.30    | 0.16-0.53 |
| Yang, Q[45] | Jiangxi           | 2004 | 18-71 | 6   | 21      | 7    | 8   | 16  | 5    | 1.24    | 0.35-4.44 |
| Zhang, H[42] | Shanghai         | 2007 | -    | 106  | 168     | 78   | 44  | 53  | 17   | 1.62    | 0.92-2.88 |
| Zhang, W[43] | Singapore        | 2007 | -    | 32   | 84      | 29   | 42  | 76  | 39   | 0.76    | 0.44-1.30 |
| Wang, J Y[27] | Taiwan           | 2009 | 7.82 ± 3.81 | 105 | 201     | 139  | 124 | 250 | 136  | 1.25    | 0.94-1.65 |
| Wu, X H[40] | Hubei            | 2010 | 8.8  | 46   | 131     | 75   | 59  | 110 | 58   | 1.23    | 0.83-1.85 |

| Table 6 Main data of all studies included in the meta-analysis for the -589 C/T polymorphism in IL-4 gene |
| Study | Population location | Year | Age | Case | Control |
|-------|---------------------|------|-----|------|---------|
|       |                     |      |     | TT   | CT      | CC   | TT  | CT  | CC  | OR     | 95%CI     |
| Cui, T P[33] | Hubei              | 2003 | 3-68 | 141  | 89      | 11   | 114 | 52  | 9    | 1.33    | 0.89-1.98 |
| Hu, S Y[36] | Guangdong          | 2005 | 2-16 | 108  | 59      | 8    | 114 | 52  | 9    | 1.16    | 0.75-1.79 |
| Liu, L N[37] | Henan              | 2005 | 3-15 | 45   | 29      | 2    | 34  | 23  | 3    | 0.90    | 0.45-1.79 |
| Mak, J C[38] | Hong Kong          | 2007 | 42.4 ± 16.1 | 179 | 95      | 15   | 186 | 87  | 19   | 1.08    | 0.77-1.51 |
| Wang, W[46] | Xinjiang           | 2004 | 39 ± 8 | 22   | 42      | 29   | 15  | 26  | 21   | 1.03    | 0.49-2.19 |
| Wu, X H[40] | Hubei              | 2010 | 8.8  | 163  | 83      | 6    | 132 | 84  | 11   | 0.76    | 0.52-1.10 |
| Zhang, W D[47] | Shanghai         | 2005 | -    | 101  | 47      | 4    | 109 | 45  | 3    | 1.15    | 0.71-1.85 |
| Wang, J Y[27] | Taiwan            | 2009 | 7.82 ± 3.81 | 279 | 145     | 22   | 309 | 183 | 16   | 0.93    | 0.72-1.21 |
### Table 7 Main data of all studies included in the meta-analysis for the -308A/G polymorphism in TNF-α gene

| Study       | Population location | Year  | Age       | GG  | GA  | AA  | GG  | GA  | AA  | OR  | 95%CI     |
|-------------|---------------------|-------|-----------|-----|-----|-----|-----|-----|-----|-----|-----------|
| Gao, J M[48]| Beijing            | 2003  | 38.7 ± 13.8 | 47  | 52  | 26  | 44  | 41  | 11  | 1.40 | 0.82-2.41 |
| Guo, Y L[49]| Jiangxi            | 2004  | -         | 4   | 28  | 16  | 7   | 11  | 3   | 1.50 | 1.00-2.16 |
| Li, Z F[50] | Guangdong          | 2003  | 2-12      | 9   | 16  | 5   | 14  | 10  | 2   | 2.72 | 0.91-8.16 |
| Liu, R M[51]| Hubei              | 2004  | 2-15      | 98  | 15  | 0   | 104 | 22  | 0   | 0.72 | 0.36-1.47 |
| Mak, J C[38]| Hong Kong          | 2007  | 42.4 ± 16.1 | 244 | 47  | 1   | 250 | 40  | 2   | 1.17 | 0.75-1.84 |
| Tan, E C[52]| Singapore         | 1999  | -         | 49  | 18  | 0   | 115 | 36  | 0   | 1.17 | 0.61-2.26 |
| Wang, T N[53]| Taiwan            | 2004  | 5-18      | 140 | 49  | 2   | 111 | 18  | 0   | 2.25 | 1.24-4.06 |
| Zhao, H J[55]| Jilin             | 2005  | -         | 45  | 5   | 0   | 71  | 9   | 0   | 0.88 | 0.28-2.78 |
| Wang, J Y[27]| Taiwan            | 2009  | 7.82 ± 3.81 | 345 | 100 | 3   | 409 | 94  | 7   | 1.21 | 0.89-1.65 |

### Table 8 Main data of all studies included in the meta-analysis for the -6843G/A polymorphism in FcεRI β gene

| Study       | Population location | Year  | Age       | AA  | AG  | GG  | AA  | AG  | GG  | OR  | 95%CI     |
|-------------|---------------------|-------|-----------|-----|-----|-----|-----|-----|-----|-----|-----------|
| Chan, I H[16]| Hong Kong          | 2008  | 10.4 ± 3.7 | 267 | 23  | 1   | 154 | 13  | 0   | 1.06 | 0.53-2.15 |
| Cui, T P[56] | Hubei              | 2004  | 40.37 ± 15.09 | 60  | 40  | 6   | 78  | 26  | 2   | 2.14 | 1.20-3.81 |
| Liu, T[57]  | Shandong           | 2006  | 36.5      | 45  | 14  | 1   | 39  | 10  | 1   | 1.18 | 0.49-2.87 |
| Tang, Y[58] | Guangdong         | 2003  | 39.5(12-67)| 49  | 11  | 0   | 61  | 4   | 0   | 3.42 | 1.03-11.42 |
| Wang, L[59] | Hubei              | 2003  | 2-16      | 65  | 40  | 5   | 70  | 20  | 2   | 2.20 | 1.20-4.06 |
| Zeng, L X[60]| Jiangxi           | 2001  | 37(14-63) | 61  | 5   | 3   | 27  | 1   | 0   | 3.54 | 0.42-29.73 |
| Zhang, X Z[61]| Singapore      | 2004  | 52 ± 16   | 81  | 57  | 3   | 108 | 42  | 7   | 1.63 | 1.02-2.62 |
| Zhao, K S[62]| Jilin             | 2004  | 1.5-14    | 126 | 23  | 2   | 92  | 13  | 0   | 1.40 | 0.68-2.89 |
| Wang, J Y[27]| Taiwan            | 2009  | 7.82 ± 3.81 | 309 | 121 | 16  | 314 | 165 | 27  | 0.73 | 0.55-0.95 |

### Table 9 Main data of all studies included in the meta-analysis for the -109C/T polymorphism in FcεRI β gene

| Study       | Population location | Year  | Age       | TT  | TC  | CC  | TT  | TC  | CC  | OR  | 95%CI     |
|-------------|---------------------|-------|-----------|-----|-----|-----|-----|-----|-----|-----|-----------|
| Li, H[19]  | Shanghai            | 2009  | 3-12      | 110 | 58  | 24  | 78  | 90  | 24  | 1.00 | 0.55-1.83 |
| Wang, L[59] | Hubei              | 2003  | 2-16      | 43  | 54  | 13  | 35  | 46  | 11  | 0.99 | 0.42-2.32 |
| Zhao, K S [63]| Jilin             | 2004  | 5.6 ± 3.1 | 46  | 69  | 11  | 40  | 38  | 9   | 0.83 | 0.33-2.09 |

### Table 10 Main data of all studies included in the meta-analysis for the D/I polymorphism in ACE gene

| Study       | Population location | Year  | Age(year) | II  | DI  | DD  | II  | DI  | DD  | OR  | 95%CI     |
|-------------|---------------------|-------|-----------|-----|-----|-----|-----|-----|-----|-----|-----------|
| Gao, J M[64]| Beijing            | 1999  | 39(16-69) | 12  | 15  | 23  | 16  | 26  | 8   | 4.47 | 1.75-11.43 |
| Guo, Y B[65]| Guangdong          | 2006  | 0.33-3    | 27  | 18  | 7   | 36  | 32  | 4   | 2.64 | 0.73-9.56 |
| Lu, H M[66] | Tianjin            | 2004  | 37(18-52)| 3   | 4   | 11  | 5   | 7   | 3   | 6.29 | 1.29-30.54 |
| Lue, K H[67]| Taiwan            | 2006  | 9.91 ± 1.62 | 48  | 40  | 17  | 56  | 42  | 4   | 4.73 | 1.53-14.60 |
| Qin, J H[68]| Liaoning          | 2000  | 6.9 ± 2.7 | 24  | 10  | 18  | 21  | 14  | 5   | 3.71 | 1.24-11.10 |
| Song, L J[69]| Jilin             | 2001  | 1-14      | 22  | 45  | 41  | 18  | 29  | 9   | 3.20 | 1.42-7.20 |

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### Table 11 Main data of all studies included in the meta-analysis for the -2044A/G polymorphism in IL-13 gene

| Study | Population location | Year | Age | Case | Control |
|-------|---------------------|------|-----|------|---------|
| Chan, I H[16] | Hong Kong | 2008 | 10.4 ± 3.7 | GG: 94, AG: 136, AA: 43 | GG: 54, AG: 70, AA: 17 |
| Feng, D[70] | Heilongjiang | 2009 | 3-16 | 17 | 18 |
| Liu, J Li[71] | Guangdong | 2004 | 14-67 | 27 | 54 |
| Wu, X H[40] | Hubei | 2010 | 88 | 105 | 111 |
| Yang, L F[72] | Gansu | 2010 | 8 ± 4 | 71 | 60 |
| Zhao, K S[73] | Jilin | 2005 | 1.5-14 | 18 | 60 |
| Wang, J Y[27] | Taiwan | 2009 | 7.82 ± 3.81 | 203 | 194 |
| Xi, D[74] | Hubei | 2004 | 20 | 10 | 15 |
| Xi, D[74] | Hubei | 2004 | ≥4 | 10 | 25 |

### Table 12 Main data of all studies included in the meta-analysis for the -1923C/T polymorphism in IL-13 gene

| Study | Population location | Year | Age | Case | Control |
|-------|---------------------|------|-----|------|---------|
| Song, Q Z[75] | Guangdong | 2005 | 14-67 | CC: 24, CT: 55, TT: 21 | CC: 43, CT: 47, TT: 10 |
| Shi, X H[22] | Jiangsu | 2008 | 34(14-66) | 12 | 26 |
| Chen, J Q[76] | Jiangsu | 2004 | 2.59 ± 1.45 | 41 | 43 |
| Wang, X H[77] | Shandong | 2009 | 39 ± 11 | 31 | 57 |
| Wu, X H[40] | Hubei | 2010 | 8.8 | 106 | 114 |

### Table 13 Main data of all studies included in the meta-analysis for the -511C/T polymorphism in IL-1β gene

| Study | Population location | Year | Age | Case | Control |
|-------|---------------------|------|-----|------|---------|
| Hsieh, C C[78] | Taiwan | 2004 | 8.74 ± 4.09 | GG: 69, GA: 40 | GG: 48, GA: 70 |
| Wu, Z F[79] | Jiangxi | 2007 | 11-68 | 16 | 36 |
| Zhao, X F[80] | Yunnan | 2006 | 5.9(3-14) | 51 | 4 |

### Table 14 Main data of all studies included in the meta-analysis for the +252A/G polymorphism in LT-α gene

| Study | Population location | Year | Age | Case | Control |
|-------|---------------------|------|-----|------|---------|
| Gao, J M[81] | Beijing | 2003 | 38.7 ± 13.8 | AA: 13, AG: 63 | AA: 49, AG: 46 |
| Ma, W C[82] | Guangdong | 2005 | 1.8-9 | 8 | 12 |
| Mak, J C[38] | Hong Kong | 2007 | 42.4 ± 16.1 | 70 | 146 |
| Tan, E C[52] | Singapore | 1999 | - | 13 | 38 |
| Xu, X[83] | Guangdong | 2003 | 18-69 | 12 | 21 |
| Huang, S C[84] | Taiwan | 2008 | 9.9 ± 4.1 | 20 | 69 |

### Table 15 Main data of all studies included in the meta-analysis for the -509C/T polymorphism in TGF-β1 gene

| Study | Population location | Year | Age | Case | Control |
|-------|---------------------|------|-----|------|---------|
| Lu, J R[85] | Jilin | 2004 | 1-13 | CC: 45, CT: 38 | CC: 30, CT: 19 |
| Mak, J C[36] | Hong Kong | 2006 | 41.0 ± 16.1 | 46 | 109 |
| Xia, W[87] | Jiangxi | 2006 | 15-60 | 22 | 26 |
**Table 16 Main data of all studies included in the meta-analysis for the -159C/T polymorphism in CD14 gene**

| Study | Population location | Year | Age | CC | CT | TT | OR   | 95%CI  |
|-------|---------------------|------|-----|----|----|----|------|--------|
| Chan, I H [16] | Hong Kong | 2008 | 10.4 ± 3.7 | 55 | 134 | 80 | 26 | 77 | 38 | 0.88 | 0.52-1.48 |
| Chen, M [88] | Guangdong | 2009 | 14-71 | 63 | 62 | 25 | 40 | 68 | 42 | 0.50 | 0.31-0.82 |
| Cui, T P [89] | Hubei | 2003 | 2-16 | 27 | 67 | 49 | 10 | 42 | 20 | 0.69 | 0.32-1.52 |
| Tan, C Y [90] | Taiwan | 2006 | - | 17 | 56 | 47 | 24 | 55 | 41 | 1.51 | 0.77-2.99 |
| Wu, X H [40] | Hubei | 2010 | 8.8 | 54 | 117 | 81 | 31 | 121 | 75 | 0.58 | 0.36-0.94 |
| Wang, J Y [27] | Taiwan | 2009 | 7.82 ± 3.81 | 160 | 230 | 57 | 177 | 236 | 96 | 0.96 | 0.73-1.25 |

**Table 17 Main data of all studies included in the meta-analysis for the T1-C/T polymorphism in ADAM33 gene**

| Study | Population location | Year | Age | TT | TC | CC | OR   | 95%CI  |
|-------|---------------------|------|-----|----|----|----|------|--------|
| Su, D J [91] | Heilongjiang | 2008 | 36.69 ± 11.53 | 63 | 78 | 40 | 117 | 29 | 5 | 8.28 | 3.18-21.59 |
| Wang, P [92] | Shandong | 2006 | 43.32 | 250 | 45 | 1 | 236 | 33 | 1 | 0.91 | 0.06-14.65 |
| Xiong, J Y [93] | Guangdong | 2009 | 6-13 | 71 | 19 | 2 | 80 | 10 | 1 | 2.00 | 0.18-22.45 |

**Table 18 Main data of all studies included in the meta-analysis for the -28G/C polymorphism in RANTES gene**

| Study | Population location | Year | Age | CC | CG | GG | OR   | 95%CI  |
|-------|---------------------|------|-----|----|----|----|------|--------|
| Liu, M [94] | Yunnan | 2005 | 7.2 ± 4.8 | 25 | 53 | 16 | 29 | 3 | 0 | 2.71 | 0.63-11.59 |
| Wang, L [95] | Hubei | 2004 | 9 ± 3 | 65 | 31 | 4 | 72 | 17 | 1 | 2.15 | 1.11-4.17 |
| Yao, T C [96] | Taiwan | 2003 | - | 134 | 39 | 9 | 83 | 23 | 1 | 1.24 | 0.71-2.17 |

**Table 19 Main data of all studies included in the meta-analysis for the -403A/G polymorphism in RANTES gene**

| Study | Population location | Year | Age | GG | GA | AA | OR   | 95%CI  |
|-------|---------------------|------|-----|----|----|----|------|--------|
| Leung, T F [97] | Hongkong | 2005 | 9.9 ± 3.4 | 60 | 53 | 16 | 37 | 21 | 8 | 1.47 | 0.81-2.66 |
| Liu, M [94] | Yunnan | 2005 | 7.2 ± 4.8 | 17 | 13 | 2 | 16 | 14 | 2 | 0.88 | 0.33-2.35 |
| Yao, T C [96] | Taiwan | 2003 | - | 98 | 65 | 19 | 60 | 41 | 6 | 1.09 | 0.68-1.77 |

**Table 20 Summary results of the meta-analysis and publications bias**

| Gene | Polymorphism | Genotype investigated | Studies Number | Effect Model | OR(95%CI) | Publication bias (Begg’s test) |
|------|--------------|-----------------------|----------------|--------------|----------|--------------------------------|
|      |              |                       |                |              |          | t     | P    |
| β2-AR | -46G/A       | GG                    | 13             | Random       | 1.02(0.75, 1.38) | -0.66 | 0.525 |
|       | -79G/C       | GG                    | 10             | Fixed        | 0.86(0.58, 1.32) | 1.60 | 0.148 |
| IL-4R | -1902G/A     | GG+GA                | 12             | Random       | 1.30(0.94, 1.80) | -0.24 | 0.777 |
|       | -223G/A      | GG                    | 7              | Random       | 0.92(0.63, 1.35) | 0.81 | 0.453 |
| IL-4  | -589G/C/T    | CC                    | 8              | Fixed        | 1.01(0.88, 1.16) | 0.53 | 0.615 |
| TNF-α | -308A/G      | AA+AG                | 10             | Random       | 1.42(1.09, 1.85) | 1.38 | 0.205 |
| FceRβ | -684G/AG     | GG                    | 9              | Random       | 1.49(1.01, 2.22) | 2.82 | 0.026 |
|       | -109C/T      | CC                    | 3              | Fixed        | 0.96(0.62, 1.48) | -1.10 | 0.471 |
| ACE   | D/I          | DD                    | 6              | Fixed        | 3.85(2.49, 5.94) | 0.88 | 0.429 |
| IL-13 | -2044A/G     | AA+AG                | 9              | Random       | 1.49(1.07, 2.08) | 1.93 | 0.095 |
|       | -1923C/T     | TT                    | 5              | Fixed        | 2.99(2.12, 4.24) | 1.19 | 0.320 |
| IL-1β | -511C/T      | TT+TC                | 3              | Fixed        | 1.10(0.76, 1.59) | -0.16 | 0.896 |
| LT-α  | +252A/G      | GG                    | 6              | Fixed        | 1.26(0.98, 1.62) | -0.02 | 0.985 |
| TGF-β1 | -509C/T     | TT+TC                | 3              | Fixed        | 1.17(0.83, 1.64) | 0.57 | 0.074 |
| CD14  | -159C/T      | TT+TC                | 6              | Random       | 0.79(0.59, 1.06) | -0.41 | 0.700 |
| ADAM33 | T1-C/T      | CC                    | 3              | Fixed        | 6.07(2.69, 13.73) | -8.22 | 0.077 |
| RANTES | -28G/C      | GG                    | 3              | Fixed        | 1.64(1.09, 2.46) | 0.87 | 0.544 |
|       | -403A/G      | AA+AG                | 3              | Fixed        | 1.18(0.83, 1.67) | -0.37 | 0.777 |
Figure 2 Forest plot of asthma risk associated with β2-AR -46G/A in Chinese population. Subgroup analysis by age.

Figure 3 Forest plot of asthma risk associated with β2-AR -79G/C in Chinese population. Subgroup analysis by age.
Figure 4 Forest plot of asthma risk associated with IL-4R -1902G/A in Chinese population. Subgroup analysis by age.

Figure 5 Forest plot of asthma risk associated with IL-4R -223G/A in Chinese population. Subgroup analysis by age.
Figure 6 Forest plot of asthma risk associated with *IL-4*-589C/T in Chinese population. Subgroup analysis by age.

Figure 7 Forest plot of asthma risk associated with *TNF-α*-308A/G in Chinese population. Subgroup analysis by age.
five polymorphisms (ACE D/I, FcεRIb-6843G/A, TNF-α-308G/A, IL-13-1923C/T, IL-13-2044A/G) in adults.

Publication bias
The Begg’s funnel plots and Egger’s tests were performed to assess the potential publication bias (Begg’s funnel plots can be seen in Additional File 1). The results did not suggest evidence of publication bias except for the FcεRIb-6843G/A polymorphism. Statistical results of Begg’s test are summarized in Table 20.

Discussion
The aim of meta-analysis is to combine results from studies on the same topic and to produce more precise results. The current study is to reveal the roles of genetic variants and their associations with risk of asthma in Chinese population. In summary, we finally identified 18 polymorphisms in 13 genes. Among them, seven polymorphisms (ADAM33 T1-C/T, ACE D/I, FcεRIb-6843G/A, IL-13-1923C/T, IL-13-2044A/G, RANTES-28C/G and TNF-α-308G/A) were statistically associated with increased risk of asthma. In order to analysis the age-specific associations, subgroup analysis were performed by age. The ACE D/I, B2-AR-79G/C, TNF-α-308G/A, IL-4R-1902G/A and IL-13-1923C/T polymorphisms were found being associated with asthma risk in Chinese children, while the ACE D/I, FcεRIb-6843G/A, TNF-α-308G/A, IL-13-1923C/T, IL-13-2044A/G polymorphisms were associated with asthma risk in Chinese adults. Given that the data
for each polymorphism were from at least three case-control studies, the obtained results could be more precise than results obtained from any individual study.

The β2-AR gene is a critical gene in the pathogenesis of asthma. β2-ARs are present on many airway cells, especially in smooth muscle cells which are hyperreactive in asthmatic patients. At present, β2-AR agonists were major methods for treating asthmatic patients. In this meta-analysis, ten case-control studies for β2-AR -79G/C and eleven for -46G/A polymorphism were identified. The results indicated the two polymorphisms were not associated with asthma risk in hasthmatic patients, and the obtained results could be more precise than results obtained from any individual study.
Chinese population. After subgroup analysis by age, the -79G/C polymorphism was associated with decreased risk of asthma in Chinese children. Up to now, three meta-analyses had been performed to investigate the association between polymorphism of β2-AR gene and risk of asthma [10-12]. Thakkinstian A[12] found that the heterozygote in -79G/C was associated with decreased risk of asthma in both adults and children. However, we didn’t find these associations in Chinese adults, which suggested different roles of this polymorphism may exist in the pathogenesis of asthma in different age groups. Previous study indicated that the -46G allele enhanced agonist-induced down regulation of the receptor, and the -79G allele might enhance resistance to down regulation. In combination with our results, personalized therapy of asthma patients in different age population with different genetic backgrounds in Chinese population should also be carried out in clinical practices.

The TNF-α gene, encodes a key proinflammatory cytokine in airway, is located on an asthma susceptible region-chromosome 6p. The TNF-α protein plays a central role in inflammation and involves in pathogenesis of asthma. Several polymorphisms have been identified in this gene, such as -308A/G, -238A/G. The -308A/G polymorphism in the promoter may affect the
expression of this cytokine, which may affect the occurrence of asthma. In the meta-analysis performed by Gao and colleagues[13], they found the A allele was significant with increased risk of asthma (OR = 1.37, 95%CI = 1.02-1.84 for A vs. G). Consistently, we found the TNF-\(\alpha\)-308A/G polymorphism was significantly associated with increased risk of asthma (OR = 1.36, 95%CI = 1.13-1.63 for AA+AG vs. GG) in Chinese population. For A vs G, the pooled OR is 1.26 with 95%CI: 1.08-1.47 in this study, which suggested a weaker association between this polymorphism and asthma risk in Chinese population.

**IL-4** gene is located on chromosome 5q31, it was suggested to be associated with asthma risk, including elevated serum IgE levels and airway hypersensitiveness. A few studies indicated the -589C/T polymorphism in the promoter as a risk factor for asthma, but with inconclusive results. Li and colleagues performed a meta-analysis and found the T allele was associated with decrease risk of asthma (T vs C: OR = 0.86, 95%CI = 0.78-0.94)[14]. However, our results didn't reveal a positive association between this polymorphism and risk of asthma in Chinese. Compared with Li's study, the total number of studies concerning the Chinese population

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**Figure 14** Forest plot of asthma risk associated with LT-\(\alpha\)+252A/G in Chinese population.

**Figure 15** Forest plot of asthma risk associated with TGF-\(\beta\)1 -509C/T in Chinese population.
Figure 16 Forest plot of asthma risk associated with CD14 -159C/T in Chinese population.

Figure 17 Forest plot of asthma risk associated with ADAM33 T1-C/T in Chinese population.

Figure 18 Forest plot of asthma risk associated with RANTES -28G/C in Chinese population.
was smaller, which suggested more studies should be carried out to reveal these associations.

IL-4 and IL-13 signal through binding to a receptor complex comprised of the IL-13Rα1 and IL-4Rα with subsequent phosphorylation of JAKs and STAT6[15]. IL-4 receptor plays its role in inflammation through IL-4 and IL-13. The IL-4 receptor gene is located on chromosome 16 p12.1-p11.2. Some polymorphisms had been identified as risk factors for asthma, such as -1902G/A and -223G/A. Our results indicated the -1902G/A polymorphism was associated with increased risk of asthma in Chinese children, but not in Chinese adults. The results also indicated the -223G/A polymorphism was not associated with risk of asthma in Chinese population.

The FcεRIb gene is a major candidate gene, involving in the pathogenesis of asthma. It is located on the chromosome 11q13. The -6843G/A polymorphism, leading change in an amino acid sequence at residue 237 from glutamic acid to glycine, is associated with increased IgE levels in atopic asthmatic children. In Chinese population, the -6843G/A polymorphism is the most extensively studied polymorphism in FcεRIb gene. Our study revealed this polymorphism as a risk factor of asthma in Chinese population. Chinese who carry the GG or GA genotype have an 49% increased risk of asthma than AA carriers. Our results also demonstrated the -109C/T polymorphism in this gene was not associated with increased risk of asthma in Chinese population.

Up to date, we first found that ADAM33 T1-C/T, ACE D/I, IL-13 -1923C/T, RANTES -28C/G and IL-13 -2044A/G polymorphisms were associated with risk of asthma in Chinese population by using meta-analyzes. Some results are similar to other studies performed in other ethnic- groups and some are not. In future, more published results should be included to update and validate these associations in Chinese population.

In this study, the rigorous inclusive criteria made the results more precise. Any study in which genotype distribution of control group divorced from HWE was excluded. In this meta-analysis, 11 polymorphisms were synthesized by using the fixed-effect model, 7 used random-effects model. Because the fixed-effect model is more precise than random effect model, the strength of evidence of ADAM33 T1-C/T, ACE D/I, IL-13 -1923C/T, RANTES -28C/G, as risk factors for asthma was greater than that of FcεRIb -6843G/A, IL-13 -2044A/G and TNF-α -308G/A.

The heterogeneity of clinical information among studies should also be mentioned. Heterogeneity is an important issue when interpreting the results of meta-analysis. Significant heterogeneity existed in overall comparisons in a few meta-analyses, such as FcεRIb -6843G/A. After subgroup analyses by age, the heterogeneity was effectively decreased or removed in adults. Possible explanation may be that differences in etiology may exist in difference age groups. Another important factor contributing to heterogeneity was that homogeneity in either the case and control groups was uncertain. Ideally, all cases and controls in this meta-analysis should be matched for age, sex, atopic status and environmental exposures. However, these issues could not all be explained precisely because of insufficient clinical information for individual person. In addition, because this study is based on population of Chinese descent with the same genetic background, so the similarity of these studies might be very good, despite most studies were conducted in different areas of China.

Some limitations of this meta-analysis should be acknowledged when explaining our results. First, only published articles in the selected electronic databases were included in this study, it may be possible that some studies were not included in those databases or some unpublished studies which had null results, which might bias the results. Second, due to lack of sufficient data, the homogeneity in either the case and control groups was uncertain and data were not stratified by other factors such as atopic status or sex. The tests for gene-environment interactions were not carried out either. Third, publication bias may affect the results.
Although P values of Begg’s test were more than 0.05 in 18 meta-analyses, we could not rule out this possibility, because for some polymorphisms, the included number of studies were relatively small. Third, this study didn’t included some polymorphisms with lack of number of studies, or polymorphisms which were not characterized as -A/B for lack of quality analysis for HWE, some polymorphisms, such as GSTM1-P/N, or HLA DR1 alleles and MHC alleles were not included, future studies should performed to analysis the effect of these polymorphism in Chinese population.

To our knowledge, this is the first and most comprehensive genetic meta-analysis to date conducted in Chinese descent for any respiratory diseases. In conclusion, this meta-analysis indicated the T1-C/T polymorphism in ADAM33 gene, the D/I polymorphism in ACE gene, the -6843G/A polymorphism in FceRIβ gene, the -1923C/T polymorphism in IL-13 gene, the -2044A/G polymorphism in IL-13 gene, the -28C/G polymorphism in RANTES gene and the -308G/A polymorphism in TNF-α gene are associated with asthma risk in Chinese population. And these results may also implicate in personalized therapy for asthma in Chinese population. In future, more studies should be conducted to investigate the gene-gene and gene-environment interactions between these polymorphisms in Chinese population.

Additional material

Additional file 1: Begg’s funnel plots for publication bias in selection of studies on asthma susceptibility genes in Chinese population. Figure S1 Begg’s funnel plots for publication bias in selection of studies on β2-AR -46G/A polymorphism. Figure S2 Begg’s funnel plots for publication bias in selection of studies on β2-AR -79G/C polymorphism. Figure S3 Begg’s funnel plots for publication bias in selection of studies on IL-4 -1902G/A polymorphism. Figure S4 Begg’s funnel plots for publication bias in selection of studies on IL-4 -223G/A polymorphism. Figure S5 Begg’s funnel plots for publication bias in selection of studies on IL-4 -589C/T polymorphism. Figure S6 Begg’s funnel plots for publication bias in selection of studies on TNF-α -308A/G polymorphism. Figure S7 Begg’s funnel plots for publication bias in selection of studies on FceRIβ -6843G/A polymorphism. Figure S8 Begg’s funnel plots for publication bias in selection of studies on FceRIβ -109C/T polymorphism. Figure S9 Begg’s funnel plots for publication bias in selection of studies on ACE D/I polymorphism. Figure S10 Begg’s funnel plots for publication bias in selection of studies on IL-13 -2044A/G polymorphism. Figure S11 Begg’s funnel plots for publication bias in selection of studies on IL-13 -1923C/T polymorphism. Figure S12 Begg’s funnel plots for publication bias in selection of studies on IL-13 -1923C/T polymorphism. Figure S13 Begg’s funnel plots for publication bias in selection of studies on IL-13 -1923C/T polymorphism. Figure S14 Begg’s funnel plots for publication bias in selection of studies on LT-α -252A/G polymorphism. Figure S15 Begg’s funnel plots for publication bias in selection of studies on CD14 -159C/T polymorphism. Figure S16 Begg’s funnel plots for publication bias in selection of studies on ADAM33 T1-C/T polymorphism. Figure S17 Begg’s funnel plots for publication bias in selection of studies on RANTES -28G/C polymorphism. Figure S18 Begg’s funnel plots for publication bias in selection of studies on RANTES -403A/G polymorphism.

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doi:10.1186/1465-9921-11-129

Cite this article as: Li et al.: Asthma susceptible genes in Chinese population: A meta-analysis. *Respiratory Research* 2010 11:129.

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