Association between β2-Adrenoceptor Gene Polymorphisms and Asthma Risk: An Updated Meta-Analysis

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Abstract

Background: Evidence is increasingly accumulated about multiple roles for the β2-adrenoceptor gene in asthma. The results were inconsistent partly due to small sample sizes. To assess the association between β2-adrenoceptor gene polymorphisms and asthma risk, a meta-analysis was performed.

Methods: We comprehensively searched the PubMed, EMBASE, BIOSIS Previews databases and extracted data from all eligible articles to estimate the association between β2-adrenoceptor gene polymorphisms and asthma risk. The pooled odds ratio (OR) with 95% confidence intervals (CIs) were calculated.

Results: Thirty-seven studies involving 6648 asthma patients and 15943 controls were included in the meta-analysis. Overall, significant associations were found in allelic genetic model (OR = 1.06, 95% CI = 1.01–1.12), recessive genetic model (OR = 1.11, 95% CI = 1.02–1.21) for Arg/Gly16. Stratified by ethnicity and age, significant associations were also found in Asian population in allelic genetic model, recessive genetic model and additive model. For Gln/Glu27, no significant association was found when we combined all eligible studies. Age stratification showed significant associations in adults in allelic genetic model and recessive genetic model, but no significant association was found among Asians and Caucasians in ethnicity stratification.

Conclusions: This meta-analysis implied that the β2-adrenoceptor Arg/Gly16 polymorphism was likely to contribute to asthma risk in Asian population. Gln/Glu27 polymorphism might be a contributor to asthma susceptibility for adults.

Introduction

Asthma is a common chronic disorder of the airways, which is characterized by airway hyperresponsiveness, obstruction, and airway wall remodeling [1]. Based on data from World Health Survey, To T and colleagues found that the global prevalence of doctor-diagnosed asthma in adults was estimated at 4.3% [2]. The prevalence reported in several studies indicated that asthma may still be increasing in western countries and developing countries [2–4]. Asthma is a complex disease and has a strong genetic component in its pathogenesis. So far, considerable efforts have been made to evaluate the association between genetic variants and asthma risk, and numerous genes have been identified as asthma susceptible genes [5–7].

The β2-adrenoceptor (β2AR) mediates the physiological responses in the airway, which include bronchodilation, broncho-protection, enhanced mucociliary clearance [8]. The β2AR gene is located on chromosome 5q31-q32, a region that is genetically linked to asthma and related phenotypes [9]. There are three best-known polymorphisms in the coding region of the β2AR gene that can modulate the function of the receptor [10]. Many studies have investigated these polymorphisms to assess their potential contributions to the risk of asthma. It was observed in some studies that β2AR gene may play a significant role in the pathogenesis of asthma [11–16]. However, other studies showed no association between asthma and β2AR gene polymorphisms [17–22]. A large population-based study and three meta-analyses have also shown inconsistent results [23–26]. Since then, additional many studies with large sample sizes about β2AR polymorphisms on asthma risk have been reported.

Therefore, we present the results of a comprehensively updated meta-analysis of all relevant published data to investigate the association between β2AR gene polymorphisms and asthma risk with focus on Arg/Gly16 and Gln/Glu27 polymorphism.

Materials and Methods

Publication search

We followed criteria of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) to perform this meta-analysis [Dox S1]. Two investigators (H.X. and Y.H.) independently carried out a systematic search of the PubMed,
EMBASE, BIOSIS Previews databases for articles published until 3 January, 2014 to identify potentially relevant articles. The search strategy utilized in our study were as follows: “asthma or bronchial asthma or bronchial hyperreactivity or allergy or atopy” and “ADRB2 or β2-adrenergic or beta adrenergic or adrenergic or adrenoceptor or beta2 AR” and “polymorphism* or variant* or genetic* or mutant*”. No publication language restrictions were imposed. All the searchable studies were retrieved, and we also checked their references for other relevant publications. The detailed search strategy for this study is shown in Box S2.

Inclusion and Exclusion Criteria
The inclusion criteria of our study were as follows: (1) Human studies evaluating associations between β2-Adrenoceptor gene polymorphisms and asthma risk, (2) There were at least two comparison groups, for example, asthma versus control (non-asthma) group, and (3) Genotype distributions in comparison groups should be available for estimating an odds ratio (OR) with 95% confidence interval (CI). Studies would be discarded if they met one of the following criteria: (1) Not relevant to β2-Adrenoceptor polymorphisms or asthma risk, (2) The design based on family or sibling pairs, (3) Reviews or abstracts without useful information. If the same patient population was reported in several publications, we included the most complete study in our meta-analysis. If original genotype frequency data were not reported, we sent an email to the corresponding author for additional data. Studies were excluded from our meta-analysis if their authors did not provide us with related data.

Data Extraction
In the data collection process, two investigators (H.X. and Y.H.) independently examined full manuscripts of eligible studies, and relevant data were extracted into predesigned data collection form. We verified accuracy of data by comparing collection forms from each investigator. Any disagreement was resolved by discussion, or a third author (Y.C.) would evaluate these articles. The following information was collected from each eligible study: first author’s name, year of publication, original country, ethnicity, sample size, genotyping method, age, and genotype numbers in cases and controls.

Publication Bias
Publication bias of studies was assessed using funnel plot, and P<0.05 was considered statistically significant. In addition, publication bias was also evaluated via Egger’s linear regression test.

Statistical analysis
We tested the Hardy-Weinberg equilibrium (HWE) in control group using the Chi-square test. The pooled ORs were calculated for allelic genetic model, additive genetic model, dominant genetic model and recessive genetic model, respectively. Subgroup analyses were performed in term of ethnicity and age. The heterogeneity between the studies was investigated by using Cochrane Q-test. I² was also used to test the heterogeneity among the included studies. A p value>0.10 for the Q-test indicates a lack of heterogeneity among the studies, then the pooled OR estimate of each study was calculated by the fixed effect model. Otherwise, the random effect model was used.

Statistical analyses were performed using the Revman5.2 software (Nordic Cochrane Center, Copenhagen, Denmark), STATA 12.0 software (Stata Corporation, College Station, TX). A p value<0.05 was considered statistically significant, except for test of heterogeneity where a level of p value<0.10 was used.

Results
Characteristics of studies included in the Meta-analysis
The flow chart in Figure 1 outlined the study selection process. A total of 2205 articles were identified at the initial search. 730 duplicated studies were eliminated first. After reading the abstracts and titles, 1320 articles were subsequently excluded. The remaining 155 articles were then assessed for inclusion and 120 articles were excluded (98 records excluded for irrelevance, 15 records no detailed genotypes, 4 depart from HWE, 3 duplicate publications). In this process, study references were checked as well and 2 relevant publication were identified [20,27]. Finally, a total of 37 studies met the inclusion criteria, and were included in the meta-analysis [11–22,27–51]. These eligible studies contained 6648 asthma cases and 15943 controls, and 11 Caucasian, 18 Asian and 8 other populations. The distributions of the β2AR gene polymorphism in normal controls were consistent with HWE in every study. Details of each study included in this meta-analysis were summarized in Table 1.

β2AR Arg/Gly16 and Asthma Risk
Among 37 studies included in the meta-analysis, 29 investigated the contribution of β2AR Arg/Gly16 polymorphism to asthma risk (Table S1). Overall, slightly significant associations were found in allelic genetic model (OR = 1.06, 95% CI = 1.01–1.12, p = 0.02), additive genetic model (OR = 1.11, 95% CI = 1.02–1.21, p = 0.02) for Arg/Gly16. Stratified by ethnicity, significant associations were also found in Asian population in allelic genetic model (OR = 1.14, 95% CI = 1.05–1.23, p = 0.001), recessive genetic model (OR = 1.26, 95% CI = 1.12–1.43, p = 0.008) and additive model (OR = 1.23, 95% CI = 1.06–1.44, p = 0.0001), but not in Caucasian population. No association was found in adults and children subgroup in term of age (Table 2).

β2AR Gln/Glu27 and Asthma Risk
There were 22 studies investigating the association between Gln/Glu27 polymorphism and asthma risk (Table S2). One study [32] may be the main contributor to heterogeneity and has significantly influenced pooled results (discuss below). Therefore, it was not included in data synthesis process. Overall, no significant association was found in all genetic models when combined all other 21 studies (Table 3). Age stratification showed significant associations in adults in allelic genetic model (OR = 1.10, 95% CI = 1.01–1.19, p = 0.03) and additive genetic model (OR = 1.20, 95% CI = 1.07–1.34, p = 0.002), but no association was found in ethnicity stratification (Table 3).

Heterogeneity exploration and sensitivity analysis
For β2AR Arg/Gly16 polymorphism, there were statistically significant heterogeneities in all genetic models when all eligible studies were combined (Table 2). We thus performed subgroup analysis on the basis of age and ethnicity. Statistically significant heterogeneity remained shown in Asian and Caucasian population subgroup, children subgroup and adults subgroup (Table 2). Therefore, we used Galbraith plots to graphically evaluate the source of heterogeneity. As showed in Figure 2A, four studies [31,35,47,50] may be the main contributor to the heterogeneity in Asian population subgroup, and Figure 2B indicated that one study [15] maybe the main contributors to the heterogeneity in Caucasian population subgroup. In order to assess the reliability of our meta-analysis, we further performed a sensitivity analysis.
through sequentially excluded individual study and similar result was obtained.

For β2AR Gln/Glu27 polymorphism, statistically significant heterogeneity were found in all genetic models, but quantitatively moderate heterogeneity with $I^2$ values<50% (Table 3). Sensitivity analysis through sequentially excluded individual study shown that one study [32] maybe the main contributor to heterogeneity and has significantly influenced pooled results. Combined results excluding this study showed small heterogeneity for both Asian and Caucasian population (Table 3).

Publication bias

For β2AR Arg/Gly16 polymorphism, as shown in Figure 3A, the shape of funnel plot revealed asymmetry to some extent. For β2AR Gln/Glu27 polymorphism, the shape of funnel plot did not indicate any evidence of significant asymmetry (Figure 3B). However, the Egger's test yielded no evidence of publication bias for β2AR Arg/Gly16 polymorphism (A vs G, p = 0.357), and Gln/Glu27 polymorphism (A vs G, p = 0.764).

Discussion

Asthma is a public health problem, affecting approximately 300 million people worldwide [32]. The mainstay of treatment for acute asthma includes inhaled short-acting β2-adrenergic receptor (β2AR) agonists, such as albuterol [5,53]. There is mounting evidence that polymorphisms in the β2AR gene are associated with significant variability in response to short-acting β2-agonists (SABA). In adults, genetic variations in this receptor have also been linked to asthma severity [12,54]. In children, significant association was observed between favorable therapeutic response to inhaled β2-adrenergic agonists and the Arg/Arg phenotype at position 16 of the β2AR [55]. However, a large cohort study has shown that important β2AR gene polymorphisms are not main determinants of asthma incidence or prevalence in the British population [25]. Therefore, conflicting data regarding the role of β2AR polymorphisms in asthma susceptibility and presentation has been reported.

We performed a systematic review and meta-analysis, including 37 studies involving 6648 asthma patients and 15943 controls, to investigate the associations between β2AR Arg/Gly16 and Gln/Glu27 polymorphisms and asthma. The combined results of 29 studies showed that A allele carriers of Arg/Gly16 polymorphism is strongly associated with asthma risk in the total population. Stratification by ethnicity revealed statistically significant association in the Asian population. Nonetheless, overall we failed to find any association between Gln/Glu27 polymorphisms and asthma risk for 21 eligible studies. Subgroup analysis on the basis of age and ethnicity showed significant associations in adults in allelic genetic model and recessive genetic model for Gln/Glu27. However, no association was found in Asian and Caucasian population subgroup based on ethnicity under any genetic model. Sensitivity analyses through sequentially excluding individual study yielded similar results in both β2AR Arg/Gly16 and Gln/Glu27 polymorphisms. In our study, we could not assess haplotype effects, which would have required genotype data that were unavailable in the published studies.

So far, three previous meta-analyses have been conducted to explore the function of β2AR gene polymorphisms in asthma [23,24,26]. One of them shown that the Gly16 allele of the β2-adrenergic receptor gene increases the risk of nocturnal asthma, but does not alter the risk of mild asthma [24]. The other reported that Gly16 may have a protective effect for children and Glu27 carriers may decrease the risk of asthma [23]. The third one showed that ADRB2 does not contribute to susceptibility of asthma [26]. Interestingly, our meta-analysis results are different from those of published meta-analyses, showing that Arg16 may increased the risk of asthma in total population, especially for Asian population. For Gln/Glu27, significant associations could only be found in adults in allelic genetic model and recessive genetic model. The inconsistency between the results of ours and published articles may be partly attributed to the following factors. First of all, while in our meta-analysis 37 studies (29 for Arg/Gly16 and 21 for Gln/Glu27, respectively) involving 6648 asthma patients and 15493 controls were included, Migita,O [26] included 8 studies for Arg/Gly16 and 9 for Gln/Glu27, Thakkinstian,A and colleagues [23] only included 12 studies for Arg/Gly16 and 12 for Gln/Glu27, Contopoulos-Ioannidis,D.G [24] included 17 studies for Arg/Gly16 and 16 for Gln/Glu27.
Table 1. Characteristics of studies included in meta-analysis.

| First author | Year | Country   | Ethnicity | Case (n) | Control (n) | Study design | Age group       | Genotyping Method |
|--------------|------|-----------|-----------|----------|-------------|---------------|------------------|-------------------|
| Abdul Vahab Saadi | 2013 | India      | Asian     | 150      | 150         | Case-control  | Mixed            | Sequencing       |
| Al-Rubaish A.#  | 2011 | Saudi Arabia | Arabia    | 73       | 85          | Case-control  | Children         | PCR-RFLP         |
| Barri RG.#      | 2001 | USA        | Caucasian | 171      | 137         | Case-control  | Adults           | Allele specific  |
| Bhatnagar, P.#  | 2005 | India      | Asian     | 101      | 55          | Case-control  | Adults           | Sequencing       |
| Binaei S.#      | 2003 | USA        | Caucasian | 38       | 155         | Case-control  | Children         | PCR-RFLP         |
| Birbian N.#     | 2012 | India      | Asian     | 410      | 414         | Case-control  | Adults           | PCR-RFLP         |
| Chan IH.#       | 2008 | China      | Asian     | 295      | 173         | Case-control  | Children         | PCR-RFLP         |
| ChiangCH.#      | 2012 | China      | Asian     | 476      | 115         | Case-control  | Adults           | PCR-RFLP         |
| Dewar JC.#      | 1998 | UK         | Caucasian | 117      | 511         | Cross-section | Adults           | Allele specific  |
| Gao G.#         | 2000 | China      | Asian     | 58       | 89          | Case-control  | Adults           | PCR-RFLP         |
| Gao JM.#        | 2002 | China      | Asian     | 125      | 96          | Case-control  | Adults           | PCR-RFLP         |
| Hakonarson H.#  | 2001 | Iceland    | Caucasian | 324      | 199         | Case-control  | Adults           | Sequencing       |
| Holloway JV.#   | 2000 | New Zealand | Caucasian | 154      | 91          | Case-control  | Adults           | Sequencing       |
| Hopes E.#       | 1998 | UK         | Caucasian | 102      | 317         | Cross-section | Children         | Allele specific  |
| Isaza C.#       | 2012 | Colombia   | NA        | 109      | 137         | Case-control  | Children         | Sequencing       |
| Karam RA.#      | 2013 | Egypt      | African   | 90       | 110         | Case-control  | Adults           | Allele specific  |
| Kohyama K.#     | 2011 | Japan      | Asian     | 300      | 100         | Case-control  | Adults           | Sequencing       |
| Kotani Y.#      | 1999 | Japan      | Asian     | 117      | 103         | Case-control  | Adults           | Allele specific  |
| Leung TF.#      | 2002 | China      | Asian     | 76       | 70          | Case-control  | Children         | PCR-RFLP         |
| Li H.#          | 2009 | China      | Asian     | 192      | 192         | Case-control  | Children         | PCR-RFLP         |
| Lin YC.#        | 2003 | China      | Asian     | 80       | 69          | Case-control  | Children         | Allele specific  |
| Martinez FD.#   | 1997 | USA        | Caucasian | 38       | 229         | Cross-section | Children         | PCR-RFLP         |
| Matheson MC.#   | 2006 | Australia  | Caucasian | 123      | 221         | Case-control  | Adults           | ARMS              |
| Munakata M.#    | 2006 | Japan      | Asian     | 46       | 100         | Case-control  | NA               | Sequencing       |
| Pino-Yanes M.#  | 2013 | Spain      | Hispanic  | 596      | 1240        | Case-control  | Children         | iPLEX Gold assay |
| Potter PC.#     | 1993 | South Africa | African  | 22       | 30          | Case-control  | Children         | PCR-RFLP         |
| Qiu YY.#        | 2010 | China      | Asian     | 201      | 276         | Case-control  | Adults           | Sequencing       |
| Reihnsa E.#     | 1993 | USA        | NA        | 51       | 56          | Case-control  | Adults           | Sequencing       |
| Santillan AA.#  | 2003 | Mexico     | NA        | 303      | 604         | Case-control  | Adults           | PCR-RFLP         |
| Shachor J.#     | 2003 | Israel     | Arabia    | 66       | 113         | Case-control  | Adults           | PCR-RFLP         |
| Szczepankiewicz A.# | 2009 | Poland      | Caucasian | 113      | 121         | Case-control  | Children         | PCR-RFLP         |
| Tatarsky, P.F.# | 2011 | Ukraine    | Caucasian | 114      | 86          | Case-control  | Children         | Multiplexed PCR   |
| Thomsen M.#     | 2012 | Denmark    | Caucasian | 547      | 8386        | Cross-section | Adults           | PCR-RFLP         |
| Wang JY.#       | 2009 | China      | Asian     | 442      | 545         | Case-control  | Children         | Taq Man           |
| Wang Z.#        | 2001 | China      | Asian     | 128      | 136         | Case-control  | Adults           | Allele specific  |
| Ye, Y.M.#       | 2010 | Korea      | Asian     | 102      | 322         | Case-control  | Adults           | Sequencing       |
| Zheng, B.Q.#    | 2012 | China      | Asian     | 198      | 110         | Case-control  | Children         | Sequencing       |

NA, not available; PCR, polymerase chain reaction; RFLP, restricted fragment length polymorphisms; SSP, sequence.
- specific primers; SPT, skin prick test; BHR, bronchial hyperresponsiveness; TDI, toluene diisocyanate; ARMS, amplification refractory mutation system; Mixed, participants involved children and adults. doi:10.1371/journal.pone.0101861.t001
**Table 2.** Results of the pooled analyses and subgroup analyses for the β2AR Arg/Gly16 polymorphism and asthma risk.

| Variable | n   | Case/Control | Arg16 vs Gly16 | Arg16Arg vs Gly16Gly | Gly16Gly vs Arg16Gly/Arg16Gly |
|----------|-----|--------------|----------------|----------------------|-------------------------------|
|          |     |              | OR[95%CI] (p)  | P-het I²              | OR[95%CI] (p) P-het I²        |
| Overall  | 29  | 5595/15184   | 1.06[1.01,1.12] | 0.00001 64%          | 1.11[1.02,1.21] 0.0007 52%    |
|          |     |              | 0.94[0.87,1.02] | 0.12 0.006 52%        | 1.10[0.99,1.22] 0.06 <0.0001 58% |
| Ethnicity|     |              |                |                      |                               |
| Asian    | 15  | 2882/2842    | 1.14[1.05,1.23] 0.001 | 0.0001 67%         | 1.26[1.12,1.43] 0.0001 53%     |
|          |     |              | 0.91[0.81,1.04] | 0.16 0.005 55%        | 1.23[1.06,1.44] 0.008 66%      |
| Caucasian| 10  | 1726/10355   | 0.99[0.91,1.08] 0.09 | 0.002 65%          | 0.94[0.80,1.10] 0.45 40%       |
|          |     |              | 0.98[0.87,1.10] | 0.72 0.003 64%        | 0.98[0.82,1.17] 0.81 0.03 52%  |
| Age      |     |              |                |                      |                               |
| Children | 10  | 1817/3009    | 1.05[0.97,1.15] 0.23 | 0.0005 70%       | 1.11[0.96,1.28] 0.15 62%     |
|          |     |              | 0.96[0.84,1.10] | 0.58 0.010 59%        | 1.06[0.89,1.26] 0.52 0.002 66% |
| Adults   | 17  | 3582/11925   | 1.04[0.98,1.11] 0.22 | 0.003 55%         | 1.06[0.95,1.18] 0.32 35%     |
|          |     |              | 0.95[0.86,1.05] | 0.31 0.01 50%        | 1.07[0.94,1.12] 0.32 0.02 47% |

n, number of studies.
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**Table 3.** Results of the pooled analyses and subgroup analyses for the β2AR Gln/Glu27 polymorphism and asthma risk.

| Variable | n   | Case/Control | Gln27 vs Glu27 | Gln27Gln vs Glu27Glu | Glu27Glu vs Gln27Gln/ Gln27Glu |
|----------|-----|--------------|----------------|----------------------|-------------------------------|
|          |     |              | OR[95%CI] (p)  | P-het I²              | OR[95%CI] (p) P-het I²        |
| Overall  | 22  | 3363/12337   | 1.07[0.99,1.15] 0.09 | 0.03 39% | 1.11[1.01,1.23] 0.03 49%      |
|          |     |              | 1.02[0.89,1.18] | 0.64 0% | 1.02[0.87,1.20] 0.80 0%       |
| Overall# | 21  | 3060/11733   | 1.02[0.95,1.10] 0.59 | 0.50 0%   | 1.03[0.93,1.14] 0.60 9%       |
|          |     |              | 1.02[0.89,1.18] | 0.58 0% | 1.01[0.86,1.20] 0.86 0%       |
| Ethnicity|     |              |                |                      |                               |
| Asian    | 9   | 1306/1286    | 1.10[0.91,1.32] 0.34 | 0.37 8%  | 1.18[0.96,1.46] 0.18 14%     |
|          |     |              | 0.72[0.42,1.23] | 0.23 0% | 0.75[0.43,1.30] 0.31 0%       |
| Caucasian| 7   | 1367/9948    | 1.03[0.94,1.12] 0.58 | 0.20 30% | 1.02[0.89,1.17] 0.12 7%      |
|          |     |              | 1.05[0.90,1.24] | 0.51 0% | 1.06[0.88,1.28] 0.51 0.25 23% |
| Age      |     |              |                |                      |                               |
| Children | 8   | 682/1104     | 0.96[0.81,1.13] 0.63 | 0.65 0% | 0.86[0.69,1.07] 0.18 0%     |
|          |     |              | 1.21[0.86,1.73] | 0.28 0% | 1.00[0.68,1.47] 0.99 0.76 0%  |
| Adults   | 12  | 2485/10987   | 1.10[1.01,1.19] 0.03 | 0.007 57% | 1.20[1.07,1.34] 0.002 62%     |
|          |     |              | 1.01[0.86,1.18] | 0.93 0% | 1.05[0.88,1.26] 0.59 0.66 0%  |

# Pooled result not included study of Santilan, A A, n, number of studies.
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respectively. Second, some articles departing from HWE have been included in Contopoulos-Ioannidis D. G and Migita, O’s meta-analysis [24,26]. Deviation from HWE is taken as an indication that the alleles are not segregating independently, either for genetic reasons or methodological reasons [56]. Therefore, this may be a potential source of inconsistency between our study and other meta-analyses.

Genome-wide association study (GWAS) has been productive genotyping method to test a vast number of single nucleotide polymorphisms and assess their relations with complex diseases and phenotypes [57]. Since the first GWAS investigating susceptibility gene for asthma published in 2007 [58], more than ten GWAS of asthma have been performed in Caucasian, Mexican, and African-ancestry populations [51,59,60] and more recently in Japan and Singapore of Asian populations [61–63]. Nevertheless, neither an individual GWAS study nor meta-analysis of GWAS has implicated ADRB2 the susceptibility gene for asthma. In our meta-analysis, we found that neither ADRB2 Arg/Gly16 nor ADRB2 Gln/Glu27 has significant association with asthma in Caucasian population, which further confirmed the results of previous published single GWAS and meta-analysis [51,59,60]. However, significant associations were found between ADRB2 Arg/Gly16 and asthma in Asian population, and this result contrasts with the results of studies recently conducted in Japan and Singapore [61–63], in which no single nucleotide polymorphisms in ADRB2 gene was found statistically significant. To date, GWAS studies for asthma have not been conducted in Chinese subjects, we are not sure whether the genomic findings of recent studies are applicable to Chinese. Therefore, in order to further clarify the role of ADRB2 gene in the pathogenesis of asthma, in the future, more GWAS should be conducted in Asian population, and especially Chinese considering its enormous environment should be considered.

Several strengths of this meta-analysis could be listed as follows. First, we followed a rigorous protocol of systematic review, identifying data from 3 different databases comprehensively. Second, we have conducted subgroup analysis, sensitivity analysis and Galbraith plots to explore the source of heterogeneity, suggesting the reliability of our study. However, the results of our meta-analysis should be interpreted with caution due to some unavoidable limitations. First, potential heterogeneity and confounding factors may have affected the analysis. Statistically significant and quantitatively moderate-to–high heterogeneities were found in all genetic model for Arg/Gly16, even if we have found out the potential heterogeneity contributors. Second, publication bias might result in the loss of studies, which subsequently could affect the meta-analysis results. The shapes of funnel plots revealed slight asymmetry for Arg/Gly16 and we should pay attention to this point. Third, asthma is a heterogeneous group of conditions that result in recurrent, reversible bronchial obstruction [5]. As shown in Table 1 that the asthma definition varied among different articles and this may be a confounding factor. Case-control studies with clear diagnosis criteria and rigorous quality control are needed to conducted in the future. Fourth, our meta-analysis was performed in Asians and Caucasians. Thus, our results may be applicable only to these ethnic groups. Fifth, although we have tried our best to contact the corresponding authors of published original papers and meta-analyses, we still cannot gain genotypes data of several studies. Sixth, so many tests have been conducted in our meta-analysis that it is not sure whether we have found something significant by chance in this process. Finally, asthma itself is a complex and multifactorial disease and potential interactions among gene-gene and gene-environment should be considered.

Conclusion

The present meta-analysis suggests that β2AR Arg/Gly16 polymorphism may be an important genetic factor in the overall risk for developing asthma, especially in Asian population, and Gln/Glu27 polymorphisms may be a contributor to asthma susceptibility for adults. GWAS or more case-control studies with explicit diagnosis criteria and rigorous quality control are needed to support this finding in various ethnic groups.

Supporting Information

Table S1 Distribution of Arg/Gly16 genotypes among patients with asthma and controls included in the meta-analysis.

(DOC)

Table S2 Distribution of Gln/Glu27 genotypes among patients with asthma and controls included in the meta-analysis.

(DOC)

Dox S1 PRISMA 2009 Statement checklist.

(DOC)
Search strategies for this study.

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