Association between beta 2 adrenergic receptor genetic polymorphisms and salbutamol responsiveness in asthmatic patients: a meta-analysis

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October 26, 2020

Abstract

Aim: There are inter-individual variations in the impact of the Beta-2 adrenergic receptor (ADRB2) polymorphisms on salbutamol response in asthmatic patients. We performed this meta-analysis to investigate the relationship between ADRB2 Arg16Gly and Gln27Glu polymorphisms and salbutamol responsiveness. Methods: Eight cyber databases (PubMed, EMbase, Web of Science, The Cochrane Library, CBM, CNKI, WanFang Date and VIP) were searched to select eligible studies until August 2020. Odds ratio (OR) and 95% confidence interval (CI) were calculated to assess the strength of the association. Results: According to the inclusion and exclusion criteria, eight studies involving 894 patients were recruited. There was a clear relationship between the Arg16Gly polymorphism and salbutamol response [AG vs. AA: OR=1.470, 95%CI (1.046, 2.066), P=0.026; GG+AA vs. AG: OR=0.668, 95%CI (0.502, 0.889), P=0.006]. Stratified analysis by age revealed significant association in adult asthmatics [AG vs. AA: OR=1.894, 95%CI (1.262, 2.843), P=0.002; GG+AA vs. AG: OR=0.597, 95%CI (0.426, 0.837), P=0.003]. Caucasian and Asian patients with the AG genotype showed a good response to salbutamol compared to those with the GG+AA or AA genotypes, respectively. However, the association among the Gln27Glu polymorphism and salbutamol response was not significant. Conclusions: The findings suggest that the ADRB2 gene Arg16Gly polymorphism may predict salbutamol responsiveness in asthmatic patients. The patients with the AG genotype are likely to show a greater response to salbutamol in comparison to those with the AA or GG+AA genotypes, especially in adult asthmatics. There may be no association between the Gln27Glu polymorphism and salbutamol response.

Introduction

Asthma is a chronic inflammatory disorder with a multifactorial etiology characterized by recurrent episodes of coughing, wheezing and dyspnea. Asthma is a polygenic disease with complex gene-environment interactions[1]. Currently, about 300 million people are affected by asthma worldwide of which about 250 000 people die per year[2, 3]. The prevalence of asthma varies from 0.2 to 21.0% around the world [3].

Global Initiative for Asthma (GINA) guidelines recommended inhaled β2-agonists as the first-line rescue treatment for managing acute asthma[4]. Short-acting beta-2 agonists (SABA), the most effective and widely used bronchodilators presently, are the primary options for treating acute exacerbations. Salbutamol, one of the representative drugs of SABA, is an effective medicine to relieve asthma. However, there are considerable differences in clinical response to inhaled SABA and 70-80% of the significant heterogeneity can be due to differences in genetic basis [5]. In addition, significant variability has been observed in salbutamol response. Genetic mutations can explain a considerable portion of this variation and the Beta-2 adrenergic receptor (*ADRB2*) may be a significant determinant of salbutamol responsiveness [5-7].

ADRB2 gene is an intronless gene located on human chromosome 5q31-32 encoding for the Beta 2 adrenergic receptor (ADRB2)— the molecular target for beta-2 agonists. Beta-2 agonists selectively bind to ADRB2 within the cell membrane and relax airway smooth muscle[8]. At least 80 single nucleotide polymorphisms (SNPs) in the *ADRB2* (such as Arg16Gly, Gln27Glu, Val34Met and Thr164Ile, etc.) have been identified after being resequenced in multiple populations [9, 10]. Arg16Gly (rs1042713, A285G) at nucleotide position 46 and Gln27Glu (rs1042714, C318G) at nucleotide position 79 have been extensively studied among these SNPs and well described in asthma pharmacogenetics [11, 12]. These *ADRB2* mutations change at the *ADRB2* amino acids sequence and alter receptor function, that may lead to the significant variability in the response to salbutamol[9]. Several previous association studies have investigated the relationship between *ADRB2* polymorphisms (Arg16Gly, Gln27Glu) and salbutamol responsiveness in asthmatic patients. However, the results are conflicting among different studies[13-20].

Thus, we conducted this meta-analysis to comprehensively investigate the effect of the *ADRB2* polymorphisms (Arg16Gly, Gln27Glu) on salbutamol response in asthmatic patients. Then we can identify individuals who are more likely to respond well to salbutamol and this will provide evidence for personalized or precision treatment for asthma improving the effectiveness of the management of asthma.

Materials and Methods

Literature search strategy

Meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[21]. We searched PubMed, EMbase, Web of Science, The Cochrane Library, CBM, CNKI, WanFang Date and VIP from establishment to August 2020. The search strategy included a combination of subjects and words as follows: ('asthma') AND ('albuterol' OR 'salbutamol') AND ('Receptors, Adrenergic, beta-2' OR '*ADRB2* ' OR 'adrenergic receptor' OR 'Beta 2 Adrenergic Receptors' OR 'Receptors, beta-2 Adrenergic' OR 'Receptors, beta 2 Adrenergic') AND ('polymorphism' OR 'SNP' OR 'variation' OR 'variant' OR 'mutation'). To find previously unconfirmed studies, we also searched references cited in the relevant articles manually. The search results were limited to human.

Study selection

The studies we included have to satisfy the inclusion criteria, as follows: (1) observational studies; (2) studies evaluated the relationship among *ADRB2* polymorphisms (Arg16Gly, Gln27Glu) and salbutamol responsiveness in asthmatic patients; (3) studies offered valid data for calculating odds ratio (OR) and 95% confidence interval (CI); (4) studies reported short-term differences in the percentage change in FEV_1 after salbutamol inhalation; and (5) human subjects. The following studies were excluded: (1) studies contained duplicate or unqualified data; (2) review, commentary, abstract, editorial, case report, letter and conference report; and (3) studies did not report the details for the assessment of good responders.

Quality assessment

Two independent reviewers conducted the methodological quality assessment of each study according to the quality of genetic studies (Q-Genie) tool which was developed by Sohani *et al.*[22] in 2015 and subsequently validated. This tool consists of 11 items scored on a 7-point Likert scale specifically applicable to the quality assessment of published genetic association studies [22, 23]. In studies without control groups, scores [?]32 indicate poor quality studies, 33-40 indicate moderate quality studies, and >40 indicate good quality studies. For studies with control groups, scores for the parameters listed above are [?]35, 36-45, and >45, respectively[22].

Data extraction

Two independent reviewers extracted the related information. The raw data of interest included name of the first author, publication year, country, ethnicity, age, salbutamol dose, genotyping method, genotype frequency distributions.

Statistical analysis

Data analysis was conducted using STATA 15.0 (StataCorp, College Station, TX, USA) software. Six genetic models were analysed, as for Arg16Gly polymorphism, namely, the dominant model (GG+AG vs. AA), recessive model (GG vs. AG+AA), allele model (G vs. A), homozygous model (GG vs. AA), heterozygous model (AG vs. AA) and additive model (GG+AA vs. AG). We tested whether genotypic frequencies fall within the Hardy-Weinberg equilibrium (HWE) by the Chi-square test. The impact of*ADRB2* polymorphisms (including Arg16Gly ,Gln27Glu) on the response to salbutamol in asthmatic patients was measured by odds ratio (OR) and 95% confidence interval (CI). The chi-square-based Cochran's Q-test and Higgins (I^2) statistics were used to assess heterogeneity among studies. The random effects model was adopted in case of evident heterogeneity (P_H<0.10 or I^2>50%). If no obvious heterogeneity existed, the fixed effects model was applied (P_H[?]0.10 and I^2[?]50%). To address significant heterogeneity, subgroup analysis and Galbraith plot analysis [24] were carried out. Subgroup analyses were performed by age (adult vs. children) and ethnicity (Caucasian vs. Asian). Sensitivity analysis was conducted by removing the study deviating from HWE. To evaluate the robustness of these results, sensitivity analysis was also employed by omitting one study at a time. Publication bias was assessed according to the asymmetry of the funnel plot. Begg's and Egger's tests [25] were also performed to evaluate publication bias and P <0.05 was interpreted as statistically significant.

Results

Study characteristics

With the searching strategy, 282 potentially relevant publications were initially retrieved. After removing duplicates and screening the titles and abstracts, we obtained 49 articles. Then we reviewed the full texts, and eight eligible studies were identified. Figure 1 shows the flowchart of the study selection. Eight studies [13-20]focused on the *ADRB2* Arg16Gly polymorphism involving 524 good responders and 370 poor responders to salbutamol. As for the*ADRB2* Gln27Glu polymorphism, five articles[13, 16, 17, 19, 20] were included with 171 good responders and 125 poor responders. Five studies [13, 15-18] included adult asthmatics, three studies[14, 19, 20] evaluated asthmatic children. Five studies [14-16, 18, 19] focused on Asian populations, and three studies [13, 17, 20]focused on Caucasian populations. The characteristics of the involved studies and HWE examination results are summarized in Table 1. The quality evaluation was carried out using the Q-Genie tool. According to the criteria for studies without control group, seven articles[13-19] were of "good quality" and one[20] presented "moderate quality" (Table 1).

Overall findings

One SNP, Arg16Gly, significant association and low heterogeneity were found between Arg16Gly polymorphism and salbutamol response in two models: heterozygous model (OR=1.470, 95% CI: 1.046-2.066,P =0.026, I^2=38.6%,P_H=0.122; Table 2 & Figure 2.5); and additive model (OR=0.668, 95% CI: 0.502-0.889, P =0.006, I^2=0.0%, P_H=0.470; Table 2 & Figure 2.6). This indicated that the patients with the AG genotype may be associated with a better response to salbutamol in comparison to those with the AA or GG+AA genotypes. However, statistically evident heterogeneity and non-significant association were detected in the dominant, recessive, allele and homozygous models (all P -value for OR>0.05). Thus, it is needed to perform further subgroup analysis and identify the sources of heterogeneity.

Concerning the *ADRB2* Gln27Glu polymorphism, non-significant association with salbutamol response was found in any models (all$P$ -value for OR>0.05) (Table 3 & Figure 3). In addition, no evidence of heterogeneity was detected between studies under five models (dominant model: I^2=35.2%,P_H=0.186; recessive model: I^2=34.9%, P_H=0.189, homozygous model: I^2=47.7%, P_H=0.105; heterozygous model: I^2=0.0%,P_H=0.452; and additive: I^2=0.0%, P_H=0.776), but not the allelic model (I^2>50%,P_H<0.1). (Table 3)

Subgroup analysis

We performed stratified analyses mainly according to age and ethnicity. Subgroup analysis by age indicated a significant relationship among*ADRB2* Arg16Gly polymorphism and salbutamol response in adult asthmatics [AG vs. AA: OR=1.894, 95% CI: 1.262-2.843, P =0.002, I^2=22.1%, P_H=0.274; GG+AA vs. AG: OR=0.597,

95% CI: 0.426-0.837, P =0.003, I^2=21.6%, P_H=0.277]. However, this relationship disappeared in asthmatic children (Table 2).

When studies were stratified by ethnicity, in Caucasian populations, patients with the AG genotype compared to the GG+AA genotypes showed a good response to salbutamol [GG+AA vs. AG: OR=0.380, 95%CI (0.198, 0.728), P =0.004, I^2=25.8%,P_H=0.260]. In Asian populations, patients with the AG genotype compared to the AA genotype were associated with a better response to salbutamol [AG vs. AA: OR=1.472, 95%CI (1.018, 2.128), P =0.040, I^2=29.0%,P_H=0.228] (data not shown). Concerning the*ADRB2* Gln27Glu polymorphism, no effect on the response to salbutamol was observed when studies were stratified by age or ethnicity under any genetic models (Table 3).

Heterogeneity analysis

For the *ADRB2* Arg16Gly polymorphism, the heterogeneity remained high in the dominant, recessive, allele and homozygous models. To further identify the sources of heterogeneity, Galbraith plots were generated in four genetic models. Galbraith plot analysis identified one outlier [18] that was outside the CI in the dominant model, and two [13, 18] in the recessive, allele and homozygous models which might contribute to the high heterogeneity (Figure 4). After removing these outliers, the heterogeneity was significantly reduced. However, the relationship between Arg16Gly polymorphism and salbutamol responsiveness in these genetic models was still non-significant: dominant model (OR=1.166, 95% CI: 0.850-1.601, P =0.341, I^2=49.7%,P_H=0.063); recessive model (OR=0.887, 95% CI: 0.632-1.246, P =0.490, I^2=0.00%,P_H=0.631); allele model (OR=1.062, 95% CI: 0.858-1.314, P =0.580, I^2=32.0%,P_H=0.196) and additive model (OR=1.089, 95% CI: 0.736-1.612, P =0.671, I^2=42.3%,P_H=0.123).

Sensitivity analysis & publication bias

Sensitivity analyses were conducted through omitting one study at a time. We also conducted sensitivity analysis by removing the study deviating from HWE. No material changes of the pooled ORs were found after omitting any single study or the HWE-violating study[15] in all genetic models for Arg16Gly polymorphism and in dominant, heterozygous and additive models for Gln27Glu polymorphism. However, as for Gln27Glu polymorphism, the corresponding pooled ORs were considerably changed after deleting a single study [17] at a time in the recessive model (OR=0.348, 95% CI: 0.093-1.308, P =0.118), allele model (OR=0.700, 95% CI: 0.428-1.145, P =0.155) and homozygous model (OR=0.334, 95% CI: 0.087-1.288, P =0.111). Egger's test and Egger's test were performed to detect the possibility of publication bias. The results demonstrated that publication bias under any genetic models was inapparent (data not shown). The funnel plots showed no obvious asymmetries (Figure 5).

Discussion

The treatment options for asthma have substantially increased. Presently, inhaled beta 2 adrenergic receptor agonists, inhaled corticosteroids, leukotriene modifiers, inhaled anticholinergics, theophylline, and immunosuppressive agents are the most common medicines for the treatment of asthma [26]. With the development of small molecule therapy and various biological agents, biologic therapies such as genetic therapy will play an important role in treating asthma [26]. Among these, short-acting beta-2 agonists (SABA) are the primary choices for the therapy of acute asthma [14, 27]. SABA selectively bind to and activate ADRB2 within the cell membrane and relax airway smooth muscle, dilate the bronchi and improve airflow achieving remission of symptoms[28].

However, there is considerable variability in inhaled SABA responsiveness, 70-80% of this can be due to differences in genetic basis [5], and part of the variability may also be explained by poor compliance, irregular medication and incorrect drug selection etc [29]. Many pharmacogenetics and pharmacogenomics studies [26, 30] have been performed for assessing the association between candidate genes and the response to SABA. A significant heterogeneity has been observed in response to salbutamol [31], and *ADRB2* gene could be responsible for this which was cloned by Kobilka *et al.*[32] in 1987 located on human chromosome 5q31-32, a region that may be linked with asthma and atopy. The *ADRB2*polymorphisms change the *ADRB2* amino

acids sequence and may alter receptor function leading to the individual variability in response to salbutamol [9].

Predicting patients who are likely to respond well to salbutamol will be significant to the further development of personalized treatment. A number of studies [13, 20] have evaluated the relationship between *ADRB2* polymorphisms (Arg16Gly, Gln27Glu) and salbutamol response. However, the results of these studies are contradictory, probably contributed by ethnic and environmental differences and the varying clinical management methods between countries.

Thus, we conducted a meta-analysis to further quantitatively investigate the effect of the *ADRB2* polymorphisms (Arg16Gly, Gln27Glu) on salbutamol responsiveness. Considering different age groups might affect salbutamol responsiveness and ethnicity may be one of the factors leading to different distribution of genetic polymorphism[33-35], we performed subgroup analyses according to age and ethnicity. We observed that as for Arg16Gly polymorphism the patients especially in adult asthmatics with the AG genotype in comparison with the AA or GG+AA genotypes had a better response to salbutamol, which indicated that salbutamol may be more effective for patients with the AG genotype. The findings are consistent with the study performed by Mohamed-Hussein *et al.*[13] which revealed that 75% of patients with the AG genotype were positive responders, and 81% of patients carrying the GG genotype were poor responders. Similar to these results, Tellería*et al.* [17] demonstrated that G allele carriers and especially patients with the AG genotype were overrepresented among subjects with good responses, while patients with the A allele were more likely to represent in the group with tachyphylaxis. In addition, Martinez *et al.*[20] revealed that compared to those with the GG genotype, patients carrying the AG genotype were 2.3 times more likely to response to salbutamol, whereas contrary to our results, patients with the AA genotype were 5.3 times more likely to have a good response.

However, our conclusions are inconsistent with the findings showed in the previous meta-analysis performed by Finkelstein *et al* in 2009[36], demonstrating that patients with the AA genotype at Arg16Gly polymorphism had a positive response to salbutamol compared to those with the AG or GG genotypes. There may be the following reasons: we excluded one study [7]selected in the previous meta-analysis but might not meet the quality criteria of the Q-Genie tool which was used in this study; included more studies up to August 2020 and applied more genetic models appropriately. Consistent with the previous meta-analysis [36], our findings indicated no effect of the Gln27Glu polymorphism on salbutamol responsiveness.

Some limitations still exist in this meta-analysis: (1) Our study mainly focused on the most common variants (Arg16Gly, Gln27Glu), other polymorphisms that have also been studied in the *ADRB2* gene[26, 37, 38] could be reported to evaluate the genetic effect of *ADRB2* on salbutamol response; (2) The number of articles included in this study and the sample size particularly for the Gln27Glu polymorphism are relatively small. Thus if more datasets are available, renewed analyses could be considered; and (3) Our research was based on dichotomous data, while continuous outcomes showing the percentage change in FEV_1 before and after salbutamol inhalation were not collected.

Conclusion

Our findings suggest that the *ADRB2* gene Arg16Gly polymorphism may be a reliable predictor of the response to salbutamol in asthmatic patients. While, we found no valid evidence to support the effect of the Gln27Glu polymorphism on salbutamol responsiveness. These findings could contribute to the development of individualized treatment and improve the effectiveness of the management of asthma. However, we have to acknowledge the limited power of our study. Therefore, we call for more well-designed studies with larger sample size to accurately verify the relationship among *ADRB2* polymorphisms and salbutamol response in asthmatic patients.

Conflict of interest: The authors declare that they have no known competing financial interests or personal relationships.

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Table 1. Summary of articles included in this meta-analysis.

Study,year	Country	Ethnicity	Age group	Salbutamol dose(μg)		Genotyping method	Ge
Arg16Gly	Arg16Gly	Arg16Gly	Arg16Gly	Arg16Gly	Arg16Gly	Arg16Gly	To
Aliae Hussein, 2018 [13]	Egypt	Caucasian	Adult	200		TaqMan	32
Sahi PK, 2016 [14]	India	Asian	Children	600		PCR- RFLP	51
Bandaru S, 2015 [15]	India	Asian	Adult	200		ARMS-PCR	26
Shah NJ, 2015 [16]	India	Asian	Adult	5000		TaqMan	23
Tellería JJ, 2005 [17]	Spain	Caucasian	Adult	400		PCR- RFLP	57
Kukreti R, 2005 [18]	India	Asian	Adult	200		SNaPshot	41
Fu J, 2002 [19]	China	Asian	Children	NA		PCR- RFLP	49
Martinez FD, 1997 [20]	America	Caucasian	Children	180		PCR- RFLP	10
Gln27Glu	Gln27Glu	Gln27Glu	Gln27Glu	Gln27Glu	Gln27Glu	Gln27Glu	To
Aliae Hussein, 2018 [13]	Egypt	Caucasian	Adult	200		TaqMan	32
Shah NJ, 2015 [16]	India	Asian	Adult	5000		TaqMan	23
Tellería JJ, 2005 [17]	Spain	Caucasian	Adult	400		PCR- RFLP	57
Fu J, 2002 [19]	China	Asian	Children	NA		PCR- RFLP	49
Martinez FD, 1997 [20]	America	Caucasian	Children	180		PCR- RFLP	10

ARMS: amplification refractory mutation system; FEV_1: forced expiratory volume in 1st second; HWE: Hardy-Weinberg equilibriu; NA: relative data were not available; PCR: polymerase chain reaction; Q-genie tool: Quality of genetic association studies; RFLP: restriction fragment length polymorphism.

Table 2. Meta-analysis of association among Arg16Gly polymorphism and salbutamol responsiveness.

Subgroup/n	Genetic model	Analysis model	OR	95%CI	*P*-value(OR)	I^2	*P*-value(H)
Overall/8	GG+AG vs. AA	R	1.218	0.666-2.228	0.521	0.600	0.014
	GG vs. AG+AA	R	0.680	0.352-1.315	0.252	0.663	0.004
	G vs. A	R	0.912	0.590-1.410	0.679	0.743	0.000
	GG vs. AA	R	0.878	0.359-2.147	0.776	0.714	0.001
	AG vs. AA	F	1.470	1.046-2.066	0.026	0.386	0.122
	GG+AA vs. AG	F	0.668	0.502-0.889	0.006	0.000	0.470
Adult/5	GG+AG vs. AA	R	1.821	0.834-3.979	0.133	0.600	0.041
	GG vs. AG+AA	R	0.792	0.302-2.075	0.635	0.779	0.001
	G vs. A	R	1.068	0.575-1.984	0.835	0.807	0.000
	GG vs. AA	R	1.417	0.422-4.760	0.573	0.763	0.002
	AG vs. AA	F	1.894	1.262-2.843	0.002	0.221	0.274
	GG+AA vs. AG	F	0.597	0.426-0.837	0.003	0.216	0.277
Children/3	GG+AG vs. AA	R	0.679	0.362-1.271	0.226	0.005	0.366
	GG vs. AG+AA	R	0.533	0.263-1.078	0.080	0.000	0.711
	G vs. A	R	0.732	0.489-1.098	0.131	0.063	0.344

Subgroup/n	Genetic model	Analysis model	OR	95%CI	*P*-value(OR)	I^2	*P*-value(H)
	GG vs. AA	R	0.431	0.184-1.010	0.053	0.000	0.424
	AG vs. AA	F	0.777	0.406-1.487	0.447	0.000	0.528
	GG+AA vs. AG	F	0.895	0.520-1.538	0.688	0.000	0.996

F: Fixed effects model; R: Random effects model; OR: Odds ratio; CI: confidence interval; *P* -value(H): *P* -value for heterogeneity; *P* -value(OR): *P* -value for OR.

Table 3. Meta-analysis of association among Gln27Glu polymorphism and salbutamol responsiveness.

Subgroup/n	Genetic model	Analysis model	OR	95%CI	*P*-value(OR)	I^2	*P*-value(H)
Overall/5	GG+CG vs. CC	F	1.085	0.657-1.793	0.750	0.352	0.186
	GG vs. CG+CC	F	1.076	0.440-2.630	0.873	0.349	0.189
	G vs. C	R	0.971	0.514-1.835	0.928	0.560	0.059
	GG vs. CC	F	1.194	0.482-2.958	0.702	0.477	0.105
	CG vs. CC	F	1.103	0.655-1.857	0.711	0.000	0.452
	GG+CC vs. CG	F	0.941	0.566-1.565	0.815	0.000	0.776
Adult/3	GG+CG vs. CC	F	1.379	0.747-2.543	0.304	0.535	0.116
	GG vs. CG+CC	F	1.456	0.499-4.253	0.492	0.602	0.081
	G vs. C	R	1.212	0.484-3.037	0.682	0.699	0.036
	GG vs. CC	F	1.668	0.569-4.888	0.351	0.685	0.042
	CG vs. CC	F	1.386	0.730-2.632	0.318	0.000	0.373
	GG+CC vs. CG	F	0.821	0.442-1.528	0.534	0.000	0.819
Children/2	GG+CG vs. CC	F	0.655	0.270-1.586	0.348	0.000	0.984
	GG vs. CG+CC	F	0.452	0.070-2.937	0.406	0.000	0.357
	G vs. C	R	0.648	0.303-1.386	0.264	0.000	0.599
	GG vs. CC	F	0.433	0.064-2.955	0.393	0.000	0.377
	CG vs. CC	F	0.699	0.284-1.724	0.437	0.000	0.648
	GG+CC vs. CG	F	1.249	0.512-3.045	0.625	0.000	0.373

F: Fixed effects model; R: Random effects model; OR: Odds ratio; CI: confidence interval; *P* -value(H): *P* -value for heterogeneity; *P* -value(OR): *P* -value for OR.

Figure Legends:

Figure 1. Flowchart of the study selection.

Figure 2. Forest plots showing the genetic impact of Arg16Gly polymorphism on salbutamol response. A. Dominant model (GG+AG vs. AA); B.recessive model (GG vs. AG+AA); C.allele model (G vs. A); D.homozygous model (GG vs. AA); E.heterozygous model (AG vs. AA); F.additive model (GG+AA vs. AG); OR: Odds ratio; CI: confidence interval; Weight: weight of each study.

Figure 3. Forest plots showing the genetic impact of Gln27Glu polymorphism on salbutamol response. A. Dominant model (GG+CG vs. CC); B.recessive model (GG vs. CG+CC); C.allele model (G vs. C); D.homozygous model (GG vs. CC); E.heterozygous model (CG vs. CC); F.additive model (GG+CC vs. CG); OR: Odds ratio; CI: confidence interval; Weight: weight of each study.

Figure 4. Galbraith plot of the Arg16Gly polymorphism and salbutamol response. A. Dominant model (GG+AG vs. AA); B.recessive model (GG vs. AG+AA); C.allele model (G vs. A); D.homozygous model (GG vs. AA).

Figure 5. Funnel plots for the studies selected in the meta-analyses under the dominant model. A. Arg16Gly polymorphism; B. Gln27Glu polymorphism.

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`Figures.pdf` available at https://authorea.com/users/370299/articles/488982-association-between-beta-2-adrenergic-receptor-genetic-polymorphisms-and-salbutamol-responsiveness-in-asthmatic-patients-a-meta-analysis