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Original Article

Association of beta2-adrenoceptor polymorphisms with asthma risk and therapeutic response: a meta-analysis and systematic review

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Abstract: The contribution of beta2-adrenergic receptor (β2-AR) gene polymorphisms to the development of asthma in the population is uncertain. We performed a meta-analysis to investigate the association between β2-AR polymorphisms and asthma risk and responses to treatments with different drugs. We searched ISI, Medline (Ovid), PubMed, CNKI, Wanfang, and Weipu databases and identified relevant literature reports. Statistical analysis was performed by using the software Revman 5.0 (Cochrane Collaboration, www.cochrane.org) and Stata 12.0 (Stata Corp, College Station, TX, USA, www.stata.com). A total of 61 studies including 45 case-controls, 10 cohorts, and 6 randomly controlled trials were subjected to our meta-analysis. Our results indicated that polymorphisms of β2-AR were not a major risk factor for the development of asthma. In the subgroup analysis by age and ethnicity, no significant associations were found among asthma patients when comparing homozygotic Arg/Arg with homozygotic Gly/Gly patients. Results from other comparative genetic models also indicated the lack of associations between this polymorphism and asthma risks. Patients with the Arg16Gly genotype might not benefit from treatments with long-acting β-agonist (LABA) coupled with inhaled corticosteroid (ICS), ICS alone, LABA alone, or short-acting β-agonist (SABA). Polymorphisms of β2-AR re not a major risk factor for the development of asthma. The results of study also show a poor correlation of therapeutic responses with β2-AR polymorphism.

Keywords: Beta2-adrenergic receptor, meta-analysis, polymorphism, pharmacogenetics, polymorphism

Introduction

Asthma is an inflammatory lung disease that affects both adults and children. Its major characteristics include airway inflammation, bronchial hyper-responsiveness, epithelial damage, and airway smooth-muscle hypertrophy [1]. A correlation study identified polymorphisms that are linked to the disease outcome in both cases and controls and in a cohort. The beta2-adrenergic receptor (β2-AR) gene codes for a 413-amino-acid G protein-coupled receptor, and it is located on the long arm of chromosome 5q31.32.3 with high allelic frequency in the general population. Single nucleotide substitutions at positions 46 (A-G) and 79 (C-G) correspond to a substitution of glycine for arginine at amino acid position 16 (Arg16Gly) and glutamine to glutamate at amino acid position 27 (Gln27Glu) [2].

A large number of studies have reported a correlation between Arg16Gly and Gln27Glu mutations in the β2-AR gene and the risk of asthma, however the results are still inconclusive. Moreover, although Thr164Ile reduces the efficiency of receptor coupling with downstream effector pathways, this polymorphism (rs1800888, Ile allele frequency 1.5%) was not a major predictor of either the frequency or the prognosis of asthma. Therefore, the Thr164Ile polymorphism is not discussed in this study. Analyses of clinical trial data also suggest that the β2-AR gene can affect the response to short-acting β2-agonists (SABAs), long-acting β2-agonists (LABAs), and LABA coupled with an inhaled corticosteroid (ICS). Nevertheless, variations in sample size can lead to inconclusive results. Thakkinstian [3] performed a meta-analysis of the Gln27Glu polymorphism in adults, suggesting that heterozygotes are at a

decreased risk of asthma. In addition, the Glu/Glu genotype has a decreased risk of asthma when compared with the other genotypes in children. Contopoulos-Ioannidis [4] has demonstrated a strong correlation between Gly16 and nocturnal asthma (OR, 2.20; 95% CI, 1.56-3.11). Gly16 homozygotes have a much higher risk for having nocturnal asthma (OR, 5.15; 95% CI, 2.44-10.84) and increased asthma severity (OR, 2.84; 95% CI, 1.62-4.96) than Arg16 homozygotes. However, Hall et al. [5] showed that Arg16Gly and Gln27Glu were not risk factors for asthma patients when GlyGly16 was compared with other genotypes and when GluGlu27 was compared with other genotypes. Thomsen et al. conducted a large study that has also found negative associations with the risk of asthma [6]. Due to the small sample size and the different populations in previously published studies, large-scale studies for a more precise conclusion are highly desired. We therefore conducted the largest and latest meta-analysis on the correlation between the Arg16Gly and Gln27Glu polymorphism with asthmatic risk as well as the therapeutic responses to different treatments.

Materials and methods

Literature search

The literature search was performed using electronic databases such as Medline (Ovid), PubMed, ISI, CNKI, Wan Fang, and Weipu containing the identification of the correlation between Arg16Gly and Gln27Glu polymorphisms and asthmatic risk. The last search was made on March 12, 2013. The searching terms related to "asthma risk" included asthma AND (beta receptor or beta-2 or adrenoceptor) AND (polymorph* or mutation * or variant * or genotype*). Further searching for eformoterol, formoterol, salmeterol, budesonide, fluticasone, ciclesonide, beclo-methadone, ICS, triamcinolone, nedocromil, cromolyn, chromium, montelukast, zafirlukast, leukotriene antagonist, corticosteroid, LTRA, and LABA in PubMed and Ovid MEDLINE as the key words was conducted. Searching was performed in duplicate by two independent reviewers (Z. LL. and G. J.). Publications in all languages were included. Authors were contacted when data were not available for extraction.

Studies in our meta-analysis needed to have met the following inclusion criteria: (I) the studies should include the evaluation of Arg16Gly and Gln27Glu polymorphisms of β2-AR and asthma risk, (II) the studies should have case control studies, (III) genotype distributions should be included in both cases and the controls for estimating an odds ratio (OR) with 95% confidence interval (95% CI), (IV) genotype distributions in control population must be consistent with Hardy-Weinberg equilibrium (HWE). Accordingly, the following exclusion criteria were adopted: (I) abstracts only and reviews, (II) repeat or overlapped publications and (III) no reports of genotype frequency. The supporting PRISMA checklist is available as supporting information; see Checklist S1.

Data extraction

Two reviewers independently checked all potentially relevant studies and reached a consensus on all items. In cases of disagreement, a third reviewer is required for evaluating these articles. The following data were collected from each study: first author, year of publication, ethnicity, definition of cases, source of the control, the total number of cases and controls, and genotype distribution in cases and controls.

Quality score assessment

The quality of studies was also independently assessed by the same reviewers (Zhang, Gong), who used quality assessment scores modified from a previous meta-analysis [3]. These scores included both traditional epidemiological considerations and genetic issues. Total scores ranged from 0 (worst) to 13 (best).

Statistical analysis

For each study, we first examined whether the genotype distribution in controls fit with the Hardy-Weinberg equilibrium using an Internet-based program (http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl).

The summary statistics for the case-control or cohort studies are the odds ratio and the ratio of observed to numbers of cases, respectively. ORs were obtained by calculating the weighted-average of the logarithm of ORs, and the studies were weighted according to the inverse of the variance of the log of the OR [(log(upper 95% confidence limit)-log(lower 95% confidence limit))2/(3.92)2]. The degree of correlation between Arg16Gly and Gln27Glu polymor-

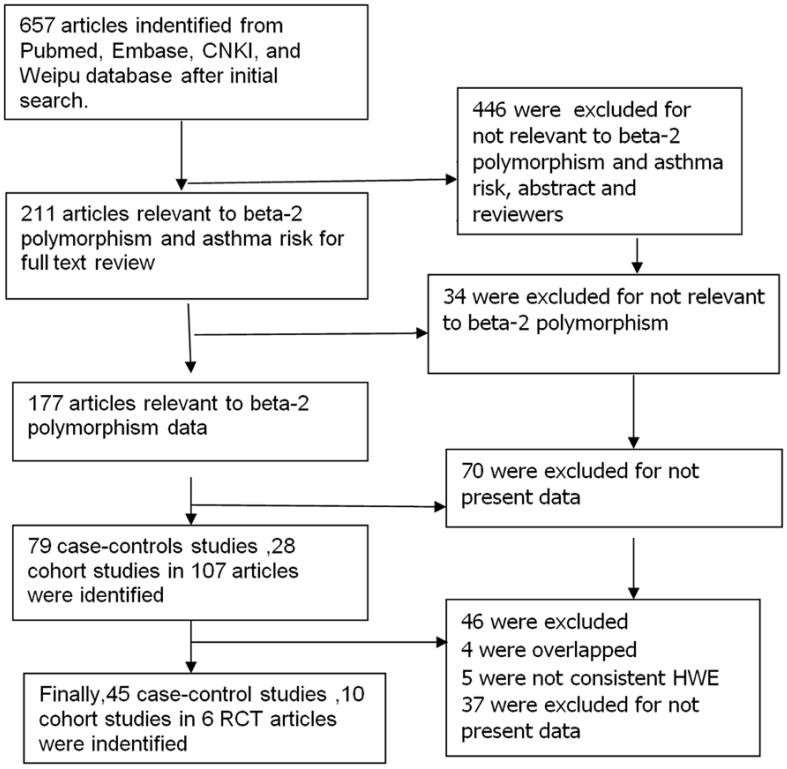

Figure 1. Flow diagram of included/excluded studies.

phisms of β2-AR and asthmatic risk was measured by OR at the 95% CI. The statistical significance of the OR was determined by Z-test. The risk of Arg16Gly was first estimated using a recessive model (Gly/Gly vs. Arg/Arg+Arg/Gly) and a dominant model (Gly/Gly+Arg/Gly/Arg/Arg), and then evaluated using a variant genotype Gly/Gly and compared with the wild-type Arg/Arg homozygote using a co-dominance model. In addition, the risks of Gly vs. Arg and Arg/Gly vs. Arg/Arg were estimated by an additive model. The evaluation of Gln27Glu was conducted in a similar fashion.

Heterogeneity was evaluated by an X^2-based Q statistical analysis and statistical significance was considered at I^2 values less than 50%. When the I^2 value is less than 50%, the pooled OR of each study was calculated by the fixed-effect model; otherwise, a random-effect model was used. The significance of the pooled OR was determined by a Z-test, and statistical significance was considered at $P<0.05$. In order to evaluate ethnicity-specific and age-specific effects, subgroup analysis was performed by age or ethnic group. Sensitivity analyses were performed through sequentially excluded individual studies to assess result stability.

Publication bias was analyzed by several methods: (I) Visual inspection of asymmetry in funnel plots; (II) Begg's test and Egger's test. All statistical tests were performed by using Revman 5.0 software and Stata 12.0.

Results

As shown in **Figure 1**, a total of 657 results were identified after an initial search. After reading the titles and abstracts, 211 potential studies were included for full-text review. After reading the full texts, 34 studies were excluded for not being relevant to the beta-2 polymorphism. Thus, 177 studies were left for data extraction. In addition, 70 studies were excluded for not presenting data. Thus, 79 case-control studies and 28 cohort studies and randomly controlled trials, giving a total of 107 articles, were identified. The genotype in the control group for 5 case-control studies was not consistent with HWE and these studies were excluded. Four case-control studies were excluded due to data overlapping or duplicated data, and 37 were excluded for not presenting data. Thus, 45 case-controls, 10 cohorts, and 6 randomly controlled trials in a total of 61 studies were identified. The characteristics of the included case-control studies are summarized in **Table 1**. Genotype and allele distributions for each case-control study are shown in **Table 2A** and **2B**. There were 28 case-control studies for Asian populations and 15 for Caucasian populations. In total, 17 studies were performed in adults, whereas 15 studies were conducted in children, and 4 studies did not report patient age. There was no overall association between the Arg16Gly polymorphism or the Gln27Glu polymorphism and the development of asthma.

Table 1. Characteristics of the 43 case-control studies included in meta-analysis

Author	Year	Country	Study design	Race	Age	Asthma type	Hardy-Weinberg X^2 values:	Quality Score
Reihsaus [49]	1993	USA	Case-Control	NA	Adults	Asthma	Yes	10
Turki [35]	1995	Colorado	Case-Control	Caucasian	Adults	Nocturnal	Yes	8
Martinez [36]	1997	USA	Cross-Sectional	Caucasian	Children	Asthma	Yes	15
Hopes [37]	1998	Britain	Cross-Sectional	Caucasian	Children	Asthma	Yes	13
Gao [7]	2000	China	Case-Control	Asian	Adults	Asthma	Yes	7
Wang [8]	2001	Taiwan	Case Control	Asian	Children	Asthma	Yes	9
Liao [9]	2001	China	Case Control	Asian	Children	Asthma	Yes	5
Hakonarson [39]	2001	Iceland	Case-Control	Caucasian	Adults	Asthma	Yes	9
Wang [10]	2001	China	Case-Control	Asian	Adults	Asthma	Yes	7
Szczepankiewicz [76]	2001	USA	Case-Control	Caucasian	Chiledren	Asthma	Yes	8
Leung [11]	2002	China HK	Case-Control	Asian	Chiledren	Asthma	Yes	12
Gao [13]	2002	CHINA	Case-Control	Asian	Adults	Nocturnal	Yes	11
Kim [14]	2002	Korea	Case-Control	Asian	Adults	Nocturnal	Yes	8
Gao [13]	2002	CHINA	Case-Control	Asian	Adults	Nocturnal	Yes	7
Ye [15]	2003	China	Case-Control	Asian	Adults	Asthma	Yes	9
Binaei [77]	2003	USA	Case-Control	Na	Children	Asthma	Yes	2
Arnaiz [40]	2003	USA	Cohort	Caucasian	Adults	Asthma	Yes	12
Shachor [48]	2003	NA	Case-Control	Jewish/Arab	Adults	Asthma	Yes	9
Barr [41]	2003	USA	Case-Control	Caucasian	Adults	Asthma	Yes	13
Santillan [42]	2003	Mexico	Case-Control	Caucasian	Adults	Asthma	Yes	13
Wang [16]	2004	China	Case Control	Asian	Adults	Asthma	Yes	5
Feng [17]	2004	China	Case Control	Asian	Adults	Asthma	Yes	9
Dai Lu-Ming [51]	2004	China	Cross-Sectional	Uk	Adults	Nocturnal	Yes	3
Litonju [43]	2004	Canada	Case-Control	Caucasian	Adults	Asthma	Yes	12
Liu [18]	2005	China	Case Control	Asian	Adults	Asthma	Yes	10
Bhatnagar [19]	2005	Indian	Case-Control	Asian	Adults	Asthma	Yes	8
Qiu [20]	2006	China	Case Control	Asian	Children	Asthma	Yes	7
Thomsen [6]	2006	Australia	Cross-Sectional	Caucasian	Adults	Asthma	Yes	14
Yin [21]	2006	China	Case-Control	Asian	Adults	Asthma	Yes	11
Wang [22]	2006	China	Case-Control	Asian	Adults	Asthma	Yes	6
Matheson [44]	2006	Australia	Case-Control	Caucasian	Adults	Asthma	Yes	10
Telleria [45]	2006	Spanish	Case-Control	Caucasian	Adults	Asthma	Yes	11
Munakata [23]	2006	Japan	Case-Control	Asian	Adults	Asthma	Yes	9
Cui [24]	2007	China	Case Control	Asian	Adults	Asthma	Yes	8
Chan [25]	2007	China	Case-Control	Asian	Chiledren	Asthma	Yes	8
Zhang [26]	2008	China	Case Control	Asian	Children	Asthma	Yes	7
Qiu [30]	2008	China	Case-Control	Asian	Adults	Asthma	Yes	6
Lee [31]	2009	China	Case Control	Asian	Children	Asthma	Yes	7
Ye [46]	2010	USA	Case-Control	Caucasian	Adults	Asthma	Yes	13
Fu [33]	2011	China	Case-Control	Asian	Adults	Asthma	Yes	7
Lee [50]	2011	China	Case-Control	Asian	Chiledren	Nocturnal	Yes	8
Al-Rubaish [34]	2011	Saudi	Case-Control	Asian	Adults	Asthma	Yes	9
Isaza [54]	2012	Colombian	Case-Control	Caucasian	Children	Asthma	Yes	13

Uk = unknown.

Quantitative data synthesis

Arg16Gly polymorphism

Asians: 20 studies [7-34] determined the correlation between Arg16Gly and asthma in Asians with sample sizes of 3,286 and 4,110 patients from asthma and control groups, respectively. We analyzed the heterogeneity of Gly/Gly vs. Arg/Arg+Arg/Gly of Arg16Gly in the Asian population from all 20 studies, and the

Table 2A. Distribution of Arg/Gly16 of ADRB2 genotype among patients with asthma and controls included in the meta-analysis

Author	Year	Arg/Gly16 polymorphism							
		Case group				Control group			
		Arg/Arg	Arg/Gly	Gly/Gly	Total	Arg/Arg	Arg/Gly	Gly/Gly	Total
Reihsaus [49]	1993	5	19	27	51	7	16	33	56
Turki [35]	1995	2	5	16	23	7	7	8	22
Martinez[36]	1997	5	18	15	38	35	108	88	231
Hopes [37]	1998	11	54	37	102	28	147	142	317
Gao [7]	2000	14	26	18	58	12	68	9	89
Wang [8]	2001	138	207	97	442	173	250	87	510
Liao [9]	2001	12	27	11	50	14	28	8	50
Hakonarson [39]	2001	45	151	127	323	21	85	75	181
Wang [10]	2001	25	54	22	101	38	64	34	136
Szczepankiewicz [76]	2001	16	48	49	113	26	54	41	121
Leung [11]	2002	25	38	13	76	22	37	11	70
Gao [13]	2002	38	59	28	125	35	53	8	96
Kim [14]	2002	34	46	23	103	89	177	100	366
Gao [13]	2002	10	23	18	51	28	36	10	74
Binaei [77]	2003	7	24	7	38	34	67	54	155
Arnaiz [40]	2003	4	5	3	12	9	11	19	39
Shachor [48]	2003	13	40	19	72	25	51	35	111
Barr [41]	2003	36	-	39	75	51	-	24	75
Santillan [42]	2003	56	163	84	303	101	318	185	604
Wang [16]	2004	48	59	16	123	26	54	9	89
Feng [17]	2004	13	35	26	74	6	28	5	39
Dai Lu-Ming [51]	2004	5	12	8	25	15	7	2	24
Litonju [43]	2004	25	76	51	152	53	176	162	391
Liu [18]	2005	6	34	2	42	6	20	4	30
Bhatnagar [19]	2005	19	54	28	101	12	30	13	55
Qiu [20]	2006	9	4	18	31	6	9	7	22
Thomsen [6]	2006	18	69	36	123	21	102	98	221
Yin [21]	2006	3	4	18	25	6	9	7	22
Wang [22]	2006	139	119	55	313	143	122	56	321
Matheson [44]	2006	18	69	36	123	21	102	98	221
Telleria [45]	2006	13	43	24	80	17	29	18	64
Munakata [23]	2006	14	21	11	46	23	47	30	100
Cui [24]	2007	9	55	8	72	12	39	9	60
Chan [25]	2007	101	135	59	295	51	89	33	173
Zhang [26]	2008	81	111	25	217	19	23	8	50
Qiu [30]	2008	25	31	14	70	34	55	23	112
Lee [31]	2009	73	100	42	215	66	78	39	183
Ye [46]	2010	44	81	36	161	84	125	53	262
Fu [33]	2011	85	88	65	238	106	92	67	265
Lee [50]	2011	3	15	9	27	10	11	3	24
Al-Rubaish [34]	2011	4	28	8	40	20	37	39	96
Isaza [54]	2012	30	39	40	109	48	42	47	137

P-value in a fixed-effect model was 0.226. In addition, the I-square value is another index of the heterogeneity test. An I-square value of 19.9% suggested low heterogeneity. Thus, we

Table 2B. Distribution Gln/Glu27 of ADRB2 genotype among patients with asthma and controls included in the meta-analysis

Author	Year	Gln/Glu 27 polymorphisms							
		Case group				Control group			
		Gln/Gln	Gln/Glu	Glu/Glu	Tatol	Gln/Gln	Gln/Glu	Glu/Glu	Total
Turki [35]	1995	7	9	7	23	4	13	5	22
Martinez [36]	1997	16	17	5	38	95	104	32	231
Hopes [37]	1998	24	63	15	102	83	156	78	317
Gao [7]	2000	32	49	8	89	20	32	6	58
Wang [8]	2001	359	84	5	448	425	77	9	511
Liao [9]	2001	26	20	4	50	20	27	3	50
Hakonarson [39]	2001	92	173	59	324	48	112	39	199
Wang [10]	2001	20	32	6	58	32	49	8	89
Szczepankiewicz [76]	2001	24	58	31	113	36	48	39	123
Leung [11]	2002	64	12	0	76	55	15	0	70
Gao [13]	2002	46	76	3	125	39	56	1	96
Kim [14]	2002	67	19	0	86	285	66	3	354
Gao [13]	2002	16	34	1	51	30	42	2	74
Ye [15]	2003	25	39	10	74	15	20	4	39
Binaei [77]	2003	23	13	2	38	107	36	12	155
Arnaiz [40]	2003	6	2	4	12	14	12	13	39
Shachor [48]	2003	38	29	5	72	50	50	9	109
Santillan [42]	2003	241	53	9	303	385	201	17	603
Wang [16]	2004	73	33	17	123	52	27	10	89
Feng [17]	2004	25	39	10	74	15	20	4	39
Dai Lu-Ming [51]	2004	23	2	1	26	22	2	1	25
Litonju [43]	2004	50	74	28	152	140	172	77	389
Liu [18]	2005	32	6	4	42	26	3	1	30
Bhatnagar [19]	2005	58	37	6	101	23	31	1	55
Qiu [20]	2006	12	18	4	34	4	7	2	13
Thomsen [6]	2006	46	56	21	123	59	109	53	221
Yin [21]	2006	4	6	24	34	5	6	2	13
Matheson [44]	2006	46	56	21	123	59	109	53	221
Telleria [45]	2006	27	39	14	80	30	20	14	64
Munakata [23]	2006	39	6	1	46	86	14	0	100
Cui [24]	2007	52	11	9	72	52	4	4	60
Chan [25]	2007	19	43	232	294	21	19	133	173
Zhang [26]	2008	54	119	44	217	8	24	18	50
Qiu [30]	2008	56	13	1	70	90	20	2	112
Lee [31]	2009	184	30	1	215	146	32	5	183
Ye [46]	2010	149	11	1	161	224	34	1	259
Fu [33]	2011	179	38	21	238	209	37	19	265
Lee [50]	2011	16	11	3	30	13	3	8	24
Al-Rubaish [34]	2011	7	11	22	40	9	31	55	95
Isaza [54]	2012	76	29	4	109	103	29	5	137

chose the fixed-effect model to synthesize the data. Overall, OR was 1.25 (1.07, 1.47), 537/2577 vs. 421/2278, I^2 = 46.3%) and the test for overall effect (P = 0.006) for dominant

Table 3. Summary of different comparative results in Arg/Gly16 (fixed model)

Genetic model	Overall or subgroup (ethnicity/age)	Study number (n)	Participant (n)	OR (95% CI)	I^2	P_{het}	P
Gly/Gly+Arg/Gly vs. Arg/Arg (dominant model)	All	36	3427/4621 vs. 4292/5698	1.156 (1.122, 1.191)	0.0%	1.000	0.000
	Asian	20	1753/2577 vs. 1533/2278	0.983 (0.892, 1.084)	0.0%	1.000	0.738
	Caucasian	14	1552/1904 vs. 2678/3270	0.987 (0.901, 1.082)	0.0%	0.992	0.784
	Adults	27	2021/2604 vs. 2611/3335	0.988 (0.910, 1.073)	0.0%	0.999	0.775
	Children	12	1389/2003 vs. 1686/2288	0.980 (0.879, 1.092)	0.0%	1.000	0.708
Gly/Gly vs. Arg/Arg+Arg/Gly (recessive model)	All	36	1194/4621 VS. 1639/5698	1.004 (0.918, 1.098)	12.7%	0.254	0.931
	Asian	20	537/2577 vs. 421/2278	0.840 (0.719, 0.981)	19.9%	0.226	0.028
	Caucasian	14	635/1904 vs. 1191/3270	1.098 (0.973, 1.240)	0.0%	0.492	0.131
	Adults*	28	762/2604 vs. 1003/3335	1.020 (0.909, 1.144)	39.5%	0.735	0.037
	Children*	12	436/2003 vs. 618/2288	0.972 (0.827, 1.142)	0.0%	0.721	0.727
Gly/Gly vs. Arg/Arg (codominant model)	All	36	1194/2428 vs. 1639/3045	1.032 (0.935, 1.139)	0.0%	0.999	0.535
	Asian	20	537/1361 vs. 421/1166	0.889 (0.751, 1.052)	0.0%	0.990	0.169
	Caucasian	14	635/987 vs. 1191/1783	1.006 (0.879, 1.152)	0.0%	0.924	0.930
	Adults	28	762/1345 vs. 1003/1727	0.971 (0.854, 1.103)	0.0%	0.935	0.649
	Children	12	436/1050 vs.618/1220	0.944 (0.792, 1.126)	0.0%	0.996	0.521
Arg/Gly vs. Arg/Arg (additive model)	All	36	1194/3387 vs. 1639/4232	0.976 (0.889, 1.072)	0.0%	0.522	0.611
	Asian	20	1216/2040 vs. 1112/1857	1.003 (0.895, 1.123)	0.0%	0.998	0.965
	Caucasian	13	1269/1904 vs. 2079/3270	0.950 (0.863, 1.046)	0.0%	0.911	0.299
	Adults	21	1330/1842 vs. 1739/2332	0.994 (0.897, 1.101)	0.0%	1.000	0.911
	Children	12	1567/1050 vs. 1670/1220	1.007 (0.905, 1.119)	0.0%	0.905	0.992
Gly vs. Aly* (additive model)	All	36	4140/8182 VS. 5433/10220	1.006 (0.972, 1.042)	0.0%	0.975	0.713

*The result is different from previous study.

Table 4. Summary of different comparative results in Gln/Glu27

Genetic model	Overall or subgroup (ethnicity/age)	Study number (n)	Participant (n)	OR (95% CI)	I^2	P_{het}	P
Glu/Glu+Glu/Gln vs. Gln/Gln (dominant model)	All	35	2006/4338 vs. 2404/5280	1.042 (0.963, 1.128)	0.0%	0.721	0.305
	Asian	21	1050/2737 vs. 702/1946	0.992 (0.962, 1.024)	0.0%	0.945	0.632
	Caucasian	14	892/1750 vs. 1634/3067	1.032 (0.997, 1.068)	14.5%	0.295	0.076
	Adults	22	1178/2525 vs. 1585/3219	1.064 (0.960, 1.180)	83.3%	0.000	0.236
	Children	12	861/1791 vs. 921/2075	0.99 (0.959, 1.029)	0.0%	0.937	0.708
Glu/Glu vs. Gln/Gln+Glu/Gln (recessive model)	All	35	608/4338 vs. 680/5280	0.91 (0.791, 1.036)	0.0%	0.971	0.149
	Asian	21	381/2737 vs. 235/1946	1.002 (0.982, 1.022)	0.0%	0.762	0.866
	Caucasian	14	219/1750 vs. 442/3067	1.212 (1.008, 1.459)	0.0%	0.998	0.041
	Adults*	22	250/2330 vs. 334/2938	1.05 (0.873, 1.263)	0.0%	0.985	0.604
	Children*	12	350/1791 vs. 343/2075	1.20 (0.986, 1.460)	0.0%	0.684	0.070
Glu/Glu vs Gln/Gln (codominant model)	All	35	608/2935 vs. 680/3556	0.945 (0.82, 1.09)	0.0%	0.989	0.436
	Asian	21	381/1697 vs. 235/1426	1.0 (1.003, 1.064)	80.3%	0.000	0.032
	Caucasian	14	673/1077 vs. 1192/3067	1.077 (0.946, 1.227)	72.3%	0.000	0.263
	Adults	22	250/1494 vs. 334/1857	1.007 (0.982, 1.032)	0.0%	0.869	0.588
	Children	12	350/1280 VS. 343/1497	1.013 (0.981, 1.045)	0.0%	0.960	0.434
Glu/Gln vs. Gln/Gln (additive model)	All	35	608/2006 vs. 680/2404	0.90 (0.76, 1.04)	0.0%	0.987	0.159
	Asian	21	669/1050 vs. 467/702	0.984 (0.928, 1.044)	0.0%	1.000	0.601
	Caucasian	14	673/892 vs. 1192/3067	0.942 (0.826, 1.075)	0.0%	1.000	0.377
	Adults	22	831/1081 vs. 1194/1415	1.004 (0.969, 1.041)	0.0%	0.996	0.821
	Children	12	350/861 VS. 343/2075	1.058 (1.004, 1.114)	0.0%	0.954	0.034
Glu vs. Gln* (additive model)	All	36	2542/8242 vs. 3013/10026	0.961 (0.916, 1.008)	7.5%	0.347	0.106

*The result is different from previous study.

Table 5. Summary of different comparative results of nocturnal asthma and non-nocturnal asthma

Type	Genetic model	Study number (n)	OR (95% CI)	I^2	P_{het}	P
Arg 16	Gly/Gly+Arg/Gly vs. Arg/Arg	7	1.234 (0.914, 1.665)	12.2%	0.337	0.169
	Gly/Gly vs. Arg/Arg+Arg/Gly	7	1.581 (1.06, 2.36) (F)	54.0%	0.054	0.024
			1.779 (0.927, 3.413) (R)	54.0%	0.054	0.083
	Gly/Gly vs. Arg/Arg	7	1.915 (1.217, 3.013)	0.0%	0.568	0.005
	Gly vs. Arg	7	1.397 (1.110, 1.758)	18.2%	0.295	0.04
	Arg/Gly vs. Arg/Arg	7	1.395 (0.964, 2.018)	0.0%	0.954	0.078
Glu27	Glu/Glu+Glu/Gln vs. Gln/Gln	7	0.933 (0.68, 1.276)	0.0%	0.851	0.663
	Glu/Glu vs. Gln/Gln+Glu/Gln	7	0.950 (0.603, 1.497)	18.6%	0.293	0.826
	Glu/Glu vs. Gln/Gln	7	0.946 (0.576, 1.55)	0.0%	0.754	0.825
	Glu vs. Gln	7	0.887 (0.64, 1.23)	34.6%	0.191	0.476
	Glu/Gln vs. Gln/Gln	7	1.043 (0.812, 1.34)	0.0%	0.820	0.743

Table 6. Distribution of haplotype frequency of Arg/Gly16 and Gln/Glu2 polymorphisms between asthma and control groups

Haplotype	Asthma (n = 1780)		Control (health group) (n = 3586)		Odds ratio	95% confidence interval
	n	%	n	%		
Arg/Gln	939	42	1541	39	1.00	
Arg/Glu	28	1	103	3	0.45	[0.30, 0.67]
Gly/Gln	652	29	1096	28	0.98	[0.93, 1.03]
Gly/Glu	628	28	1185	30	0.87	[0.83, 0.92]

model Gly/Gly vs. Arg/Arg+Arg/Gly. The results suggested that Gly/Gly homozygotes might have an increased asthma risk of 25% when compared with the homozygote Arg/Arg and the heterozygote Arg/Gly in Asian populations. As shown in **Table 3**, we also analyzed the heterogeneity of Gly/Gly vs. Arg/Arg+Arg/Gly of Arg16Gly in Asian population from all studies.

Caucasians: 14 potential articles [6, 35-47] (**Table 3**) were included, and no significant correlations were observed between Gly/Gly vs. Arg/Arg+Arg/Gly of Arg16Gly polymorphism in the Caucasian population with an OR of 0.956 (0.879, 1.040), 1058/4028vs.3950/14266, I^2 = 0.0%), and no significant difference in heterogeneity from control and case groups was found.

Children: 12 studies are included, as shown in **Table 3**. The heterogeneity of Gly/Gly vs. Arg/Arg+Arg/Gly in children was assessed(children for all 29 studies was assessed, OR was 0.972 (0.827, 1.142), 436/2003 vs. 618/2288). The I-square value was 0%, which is completely different from the study by Thakinstian [3], which found an OR of 0.71 (95% CI, (0.53, 0.96).

Adult: 20 case-control studies [6, 7, 13, 14, 16-19, 21-24, 30, 33-35, 38-46, 48, 49] were performed in adults (**Table 3**). Gly/Gly vs. Arg/Arg+Arg/Gly in Arg16Gly from adult showed an OR of 0.990 (0.912, 1.074), 1178/4783 vs. 3851/14341, I^2 = 0.0%). No significant difference in heterogeneity from the control and case groups was observed.

Gln27Glu polymorphism

Asian: There were 21 studies [7-34] addressing the correlation between Gln27Glu polymorphism and asthma in Asian populations (**Table 4**). All studies were consistent with a Hardy-Weinberg equilibrium. The heterogeneity of Glu/Glu vs. Gln/Gln+Glu/Gln in Gln27Glu polymorphism from Asian population was analyzed for all studies. The pooled risk was OR = 1.002 (0.982, 1.022), 381/2737 vs. 235/1946, I^2 = 0.0%.

Caucasian: 13 potential articles [6, 35-43, 45-47] assessed the correlation between the Gln27Glu polymorphism and asthma in adult patients (**Table 4**). All studies were consistent with the Hardy-Weinberg equilibrium, and seven studies were therefore pooled to assess the gene effect. All heterogeneity tests were negative.

Table 7. Distribution of haplotype frequency of Arg/Gly16 and Gln/Glu2 polymorphisms between hyperresponsiveness asthma and non-bronchial hyperresponsiveness asthma

Haplotype	Case (BHR+) (n = 614)		Control (BHR-) (n = 1061)		Odds ratio	95% confidence interval
	n	%	n	%		
Arg/Gln	225	37	377	36	0.95	[0.89, 1.02]
Gly/Gln	104	17	227	21	0.73	[0.61, 0.87]
Gly/Glu	284	46	453	43	1.00	

Adult: As shown in **Table 4**, the heterogeneity of Glu/Glu vs. Gln/Gln+Glu/Gln of Gln27Glu polymorphism in adults for all 19 studies revealed a *P* value of 0.991, I^2 = 0% (a fixed-effect model), and an OR of 0.965 (0.858, 1.085). The test for overall effect showed a *P* value of 0.55.

Children: Glu/Glu vs. Gln/Gln+Glu/Gln of Gln27Glu polymorphism in children for all 15 studies revealed an OR of 1.20 ((0.99, 1.46), 350/1791 vs. 343/2075) and I^2 value of 0.0%, as shown in **Table 4**. The pooled results did not exhibit any heterogeneity between procedures.

Nocturnal asthma

We further analyzed the available data on genotype comparison for the associations with nocturnal asthma [13, 14, 35, 42, 50-52]. Compared with Arg16 homozygotes, Gly16 homozygotes had a much higher risk for nocturnal asthma (OR, 1.915 (1.217, 3.013), I^2 = 0.0%). No statistically significant correlations between the Glu27 homozygote and any other phenotypes was observed, and no statistically significant heterogeneity was observed in these analyses either (**Table 5**).

Atopic and nonatopic asthma

No significant correlation was found in the asthmatic phenotype and atopy, although there were only two studies. The pooled OR for the Gly allele vs. the Arg allele was 0.828 (0.611, 1.120), I^2 = 58% in Arg16Gly. The pooled OR for Glu/Glu vs. Gln/Gln was 0.822 (0.558, 1.209) I^2 = 0% in Gln27Glu.

Haplotype analysis of Arg16Gly and Gln27Glu polymorphism

Eleven studies [14, 23, 31, 33, 42, 44, 53-57] of adults provided the data for haplotype analysis. Three [23, 56, 57] of them were on bronchial hyper-responsiveness of asthma and non-bronchial hyper-responsiveness of asthma. Haplotype frequency in asthmatic cases and controls is described in **Table 6**. Four most common haplotypes were Arg/Gln (42%), Gly/Glu (29%), Gly/Gln (28%), and Arg/Glu (1%). The estimated odds ratios were 0.45 (95% CI: 0.30, 0.67), 0.98 (95% CI: 0.93, 1.03) and 0.87 (95% CI: 0.83, 0.92) for haplotypes of Arg/Glu, Gly/Gln, and Gly/Glu when compared with Arg/Gln.

Bronchial hyper-responsiveness of asthma and non-bronchial hyper-responsiveness of asthma are shown in **Table 7**. The most common haplotypes were Arg/Gln (37%), Gly/Glu (49%), and Gly/Gln (17%). The estimated odds ratios were 0.95 (95% CI: 0.89, 1.02), 0.73 (95% CI: 0.61, 0.87), and 0.87 (95% CI: 0.83, 0.92) for haplotypes of Arg/Gln and Gly/Gln when compared with Gly/Glu. When Gln was present at position 27, the risk of asthma was lower, and the decreased risk was modified by the allele at position 16, and is lower with Gly 16 than with Arg16.

Pharmacogenetics

Drug response of short β2-agonists (SABA): Responders were defined as those with an improvement of larger than 15% or 200 mL in forced expiratory volume in 1s (FEV1) that was maintained for at least a few successive weeks. Five [12, 16, 26, 36, 45, 58, 59] studies were identified as suitable for the meta-analysis by both reviewers. All included studies focused on the positions 16 and 27, and their relationships for the acute bronchodilator response to SABA. Summary of these results during other genetic comparisons is listed in **Table 8**. A total of 2919 asthmatic patients were included in five studies, involving 548 asthmatic patients with a negative short β2-bronchodilator response and 2371 asthmatic patients with a positive bronchodilator response in asthmatic patients. A correlation between favorable therapeutic response to SABA in asthmatic patients and the Gly allele (OR = 1. 03 (0.90, 1.19)) at position 16 of the β2-AR was found when compared with Arg allele. The I square value of 63.6% using the fixed-effect model suggested hetero-

Table 8. Summary of different comparative results of responder and nonresponder

Type	Genetic model	Study number (n)	Participant (n) (case vs. control)	OR (95% CI)	I^2	P_{het}	P
Arg 16	Gly/Gly+Arg/Gly/Arg/Arg	5	1968/2371 vs. 421/548	0.995 (0.932, 1.062)	0.0%	0.978	0.884
	Gly/Gly vs. Arg/Arg+Arg/Gly	5	861/2371 vs. 196/548	1.028 (0.977, 1.082)	0.0%	0.946	0.281
	Gly/Gly vs. Arg/Arg	5	861/1264 vs. 196/304	1.014 (0.934, 1.100)	0.0%	0.723	0.742
	Gly vs. Arg	5	650/4762 vs. 656/1152	0.696 (0.622, 0.779)	63.6%	0.011	0
	Arg/Gly vs. Arg/Arg	5	1107/1510 vs. 196/421	0.89 (0.830, 0.946)	40.9%	0.149	0.000
Glu27	Glu/Glu+Glu/Gln vs. Gln/Gln	5	104/156 vs. 120/173	0.96 (0.831, 1.108)	0.0%	0.515	0.575
	Glu/Glu vs. Gln/Gln+Glu/Gln	5	62/156 vs. 53/173	0.91 (0.662, 1.246)	0.0%	0.663	0.551
	Glu/Glu vs. Gln/Gln	5	29/92 vs. 64/114	1.36 (0.721, 2.565)	0.0%	0.409	0.342
	Glu vs. Gln	5	155/312 vs. 181/346	1.117 (0.916, 1.362)	33.8%	0.275	0.196
	Glu/Gln vs. Gln/Gln	5	53/115 vs. 53/112	1.033 (0.739, 1.443)	0.0%	0.887	0.851

geneity (**Table 8**). However, all responders and non-responders from the subgroup analysis with medication (Park [58] for Tiotropium, Winterton [59] for so_2) revealed a significant decrease in risk.

Long-acting β2 agonists coupled with inhaled corticosteroid: Six studies [60-66] investigated subjects with Arg/Arg homozygotes and compared with subjects with Gly/Gly homozygotes after ICS+LABA treatment was initiated (**Table 9**). Most studies showed that patients with Arg/Arg genotype might not benefit from treatment with salmeterol or salmeterol combined with ICS. However, according to Kim's discovery, budesonide at the daily dose of 160 μg and formoterol at the daily dose of 4.5 μg could result in significantly higher FEV1, maximal mid-expiratory flow (MMEF), and better quality of life of Arg/Arg patients when compared with the control, as well as a great improvement in PEFR of Arg/Arg patients in the morning or evening. Finally, we still believe that the small sample size (n = 43) might affect the validity of the results.

Long-acting β2 agonists: Among six studies [63, 67-71] involved in the exacerbations of asthma and polymorphisms according to BTS steps of asthma management, Palmer et al. have found decreased hazard of asthma exacerbation when comparing between Gly/Gly and Arg/Arg. However, we pooled the risk of asthma exacerbation, and OR was 0.81 (0.56, 1.17) and I^2 = 0.0%, *P* = 0.27) when homozygous genotypes Gly/Gly and Arg/Arg were compared, as shown in **Table 9**. Rebordos [65] has demonstrated that no increased risk for non-controlled asthma associated with the Arg allele was observed among ICS and/or LABA users. Gly/Gly subjects had a 2-fold increase in risk of bronchial hyper-responsiveness in the absence of ICS.

Tiotropium: Park et al. [58] have showed that Arg16Gly in ADRB should be regarded as a useful marker for discriminating the response to Tiotropium. However, only one pharmacogenetic study has addressed the genetic effect on the response to Tiotropium. One of the plausible reasons is that genes coding muscarinic receptors have SNPs in their coding regions at a much lower rates than in other targets.

Discussion

Based on the data from 61 studies, this meta-analysis shows that Gly/Gly vs. Arg/Arg+Arg/Gly in the Arg16Gly polymorphism is generally not a risk factor for the development of asthma, although a 16% decrease in asthma risk in Asian population was found. Moreover, in other comparative genetic models, no significant correlation was observed in any genetic models with the Gln27Glu polymorphism. However, compared with the Arg16 homozygotes, Gly16 homozygotes have a much higher risk for nocturnal asthma. The negative therapeutic response to SABA, LABA, and ICS coupled with LABA in asthmatic patients is observed. No significant correlation was found between asthmatic phenotype and atopy.

Although Arg16 homozygotes and Gly16 homozygotes had much higher risk for nocturnal asthma by sub-analysis (odds ratio (OR) 4.63, 95% confidence interval (CI) (2.41, 8.88)), and homozygotic Arg/Arg vs. heterozygotic Arg/Gly

Table 9. Characteristics of pharmacogenetics included cohort and RCTs studies in systematic review

Author	Year	Country	Patiet Numbers (N)	Drugs	Study Design	Race	Age	Asthma Type	Hardy-Weinberg X^2 values:	Inclusion	Outcome
SAMA											
Martinez [78]	1997	Arizona	269	Albuterol	Case-control	Caucasian	Children	Wheezing	Yes	children who had at least one non-Hispanic, White (Caucasian) parent or whose parents were both Hispanic were assessed for response to a bronchodilator.	Gly/Gly VS. Arg/Arg were 5.3 times (95% confidence interval 1.6–17.7) and Arg/ArgVS. Gly/Arg for b-2AR-16 were 2.3 times (1.3–4.2) more likely to respond to albuterol
Syamsu [79]	2007	Makassar	28	Albuterol	Case-control	Asian	Adult	Asthma	Yes	Subjects were stable asthma patients who were not in exacerbation state	Arg 16 polymorphism did not have any effect on the response to terbutaline nebulation, but Gln 27 polymorphism did with OR 3.18.
Giubergia [80]	2008	Argentina	117	Albuterol: 200 mg of albuterol every 8 hr during 4 weeks	200 mg of albut erol every 8 hr during 4 weeks.	Caucasian	Children	Mild asthma	Yes	Children with diagnosis of mild intermittent and mild persistent asthma who were stable 6 months prior to the enrolment were included in the study	The homozygosity for Gln27 polymorphism was associated to a desensitization of the receptor with a decline in the bronchodilator response to albuterol after chronic use
Park [58]	2009	Korea	138	Tiotropium	Cohort	Asian	Adult	Severe asthmatics	Yes	variability of FEV1 of £ 5% over at least 8 successive weeks before enrollment	Arg16Gly in ADRB2 was associated with response to tiotropium.
Lee [50]	2011	Taiwan	51	Terbuta line Nebulizer	Cohort study	Asian	Children	Nocturnl asthma	Yes	Children with a diagnosis of asthma for at least 1 year	The polymorphisms of b2-AR 27 but not 16 or 164 were significantly associated with the response to terbutaline nebulizer ($P<0.05$)
LAMA											
Wechsler [67]	2006	USA	43	Salmeterol 18 weeks	RCT	Caucasian	Adult	Asthma	Yes	FEV1<80% predicted, or average PEF variability >20%	B16Arg/Arg subjects did not benefit compared with B16Gly/Gly subjects after salmeterol was initiated
Palmer [68]	2006	UK	546	Salmeterol 50 mg twice daily (n = 164)	Cross-sectional	Caucasian	Children	Asthma	Yes	children with physician diagnosed asthma	When patients treated with salmeterol-the homozygous genotypes, Arg/Arg and Gly/Gly were compared, an increased hazard of asthma exacerbations was founded.
Bleecker [65]	2007	USA	2630	Longacting-2agonist	Rct	Caucasian	Children	Asthma	Yes	At least 12% reversibility after 1 mg terbutaline	Gly16Arg genotype had no effect on the percentage of participants with severe exacerbations across all treatment groups.
Wechsler [63]	2009	USA	244	Salmeterol and ICS VS. Inhaled corticosteroid	RCT	Caucasian	Adult	Moderate asthma	Yes	FEV140% or more of predicted or 50% or more of predicted for patients regularly using inhaled corticosteroids	In asthma patients with B16 Arg/Arg and B16 Gly/Gly genotypes, combination treatment with salmeterol and inhaled corticosteroid improved airway function when compared with inhaled corticosteroid therapy alone.

Carroll [70]	2009	USA	37	Longacting-2agonist	Cohort study	Caucasian	Children	Severe asthmatics	Yes	Children were admitted to the hospital ICU for an asthma exacerbation	The children with the Gly/Gly genotype had significantly shorter hospital ICU length of stay and duration of continuously nebulized albuterol therapy.
Basu [71]	2009	UK	1182	Salmeterol	Cohort study	Caucasian	Uk	Asthma	Yes	Typical of children and young adults with well-controlled asthma	The risk of exacerbations observed in patients with the Arg16 allele was only observed in those receiving daily inhaled long- or short-acting b2-AR treatment; here was no genotypic risk for exacerbations in patients using inhaled b2-agonists less than once a day.
LAMA plus ICS											
Bleecker[60]	2008	USA	534	Fluticasone propionate (FP)/salmeterol 100/50 mcg (FSC) or salmeterol 50 mcg BID for 16 weeks, followed by a 2-week wash-out period	Prospective study	Caucasian	Adult	Asthma	Yes	Subjects (12 years) were randomized in equal numbers-90 per group)	Subjects with the Arg/Arg genotype experience similar improvements in asthma control without any deleterious effects compared with Gly/Gly or Arg/Gly subjects, when receiving salmeterol alone or combined with FP
Anderson [61]	2008	USA	485	Fluticasone propionate/salmeterol 100/50 mcg (FSC) or salmeterol 50 mcg	Prospective study	Caucasian	>12 years	Asthma	Yes	UK	No single polymorphism spanning the entire ADRB2 gene was associated with a consistent pattern of modulated response to salmeterol or FSC
Yancey [62]	2009	USA	218	Salmeterol plus fluticasone, 12 weeks	RCT	Caucasian	Adult	Persistent asthma	Yes	Subjects whose asthma was sub-optimally controlled with ICS, inhaled short-acting 2-agonists, or SAL and inadequately con-troled with ICS	ADRB2 Arg16Gly polymorphism does not alter lung function responses to salmeterol or FSC.
Bleecker[66]	2006	USA	183	Salmeterol, 50 m Twice-daily 12 weeks+ICS	Rct	Usa	Adult	Persistent asthma	Yes	Adult a history of persistent asthma of at least 6 months. All subjects were required to have an FEV1 of between 50% and 80% and 15% or greater reversibility after 2 puffs (180 m g) of albuterol.	Response to salmeterol does not vary between ADRB2 genotypes after chronic dosing with an inhaled corticosteroid.
Kim [64]	2009	Korean	43	ICS+LAMA: run-in period: budesonide (800 μg/day) plus terbutaline (5 μg prn); active treatment period: budesonide 160 μg and formoterol 4.5 μg b.i.d.	Prospective study	Asian	Adult	Asthma	Yes	Men and women, aged 18-55 years with a documented history of asthma for at least 6 months, no history of smoking orreported history of viral infection in the proceeding 6 weeks, and an FEV 1 of at least 60% of the predicted value	After 8 weeks of active treatment, Arg/Arg patients had significantly higher forced expiratory volume in 1 secord (FEV1) and maximal mid-expiratory flow (MMEF), better asthma control and quality of life after 24 weeks during treatment, there was a greater improvement in morning or evening PEFR in Arg/Arg patients.
Rebordosa [65]	2011	USA	604	Lama+ICS	Multicentre longitudinal cohort study	Caucasian	Children	Asthma	Yes	Diagnosed asthma in combination with having had asthma symptoms or having used asthma medication in the last 12 months.	The Arg allele was associated with poorer asthma control, a steeper lung function decline and bronchial hyperresponsiveness

in Asian populations showed an OR of 1.25 (1.07, 1.47), these results from small samples and small numbers of studies were unconvincing. When classified according to age, the individuals carrying the Arg16Gly or the Gln27Glu variant do not reveal an obvious decrease in asthma risk in both adult group and the child group. In contrast, Thakkinstian et al. [3] have demonstrated that Gln heterozygotes are at a decreased risk of asthma than other homozygotes (OR 0.73, 95% CI: 0.62, 0.87). In children, Glu/Glu genotype has a decreased risk of asthma (OR 0.60, 95% CI: 0.35, 0.99) when compared with other genotypes. Several factors could be considered to explain these findings, such as small sample sizes, selection bias, and missed information in some studies. A similar increased risk of asthma indicated that this polymorphism is associated with asthma risk, whereas age is not a major factor.

Nocturnal asthma represents a subset of asthma, which is associated with a significant decline in pulmonary function and an increase in airway inflammation at night. The observed association with nocturnal asthma may be partially due to the pharmacogenetic effect, because it was reported that Gly16 allele is also associated with poor treatment response [72]. However, the opposite correlations have also been observed in some other studies, with a more favorable response to regular application of short-acting β2-agonists and Tiotropium. Moreover, Glu27 polymorphism has not shown an obviously increased asthma risk in our study. The correlation of Gly16 allele with nocturnal asthma may reflect linkage disequilibrium with another functional polymorphisms, or may partially represent total functional variability at this locus [4].

Linkage disequilibrium under combinations of polymorphisms will occur more frequently than would be predicted purely by assessing the allelic frequency of the individual polymorphism in isolation. A haplotype analysis exploring all the polymorphisms across the locus will also show an association, but this will not be stronger than the examination of the causal polymorphism alone. From our study, these numbers indicated that, when Gln is present at position 27, the risk of asthma is the same regardless of which allele is present at position 16. With Glu at position 27, the risk of asthma is lower, and this decreased risk is modified by the allele at position 16, although Arg16 shows a lower risk than Gly16.

To search for the genetic variants that modify asthma susceptibility, multi-center asthma genome-wide association studies (GWAS) were carried out, and they provided different statistical evidences for the association of β2-AR gene with asthma. Some studies [73, 74] indicated that the β2-AR gene had no association with asthma. Our data also indicated that Arg16Gly and Gln27Glu were not a risk factors for the development of asthma. At the same time, there are increasing numbers of reports describing the degree of polymorphism within the coding region of the genes and its correlation with the therapeutic response for asthma. Bleecker et al. [69] showed there was no evidence that the Gly16Arg genotype was responsible for the therapeutic outcome, including asthma exacerbations and day-to-day asthma control measures. Our data also confirmed their results.

Some studies have shown that Arg16Gly patients subjected to combinatorial therapy with ICS and LABA may exhibit equal effects on the patients with the Gly/Gly polymorphism, suggesting that inhaled steroids may protect the patients from the potential pharmacogenetic effects driven by this locus [66]. Another important issue is whether all of the effects at this locus are driven by the Arg16Gly polymorphism or whether this is just a marker for a haplotype-driven treatment response. Because linkage disequilibrium is strong across this region, the majority of Caucasian individuals with Arg16 allele have a single haplotype when other SNPs at this locus are examined. However, we still believed that the Arg16Gly polymorphism does not affect the therapeutic outcome.

The limitations of this meta-analysis should also be addressed. First, some studies are excluded due to the absence of the original genotype number or frequencies, which may lead to selection bias. Meanwhile, the original data cannot be obtained in some studies. Thus, these studies are usually excluded. Second, all eligible studies are published in English and Chinese from selected databases. It is possible that some relevant studies published in other languages are missed. Third, most studies are

for Asians and Caucasians; thus, our study may be applicable to non-Africans only. Fourth, asthma is a heterogeneous disease [75], and the therapy may be affected by genetic associations with asthma phenotypes in addition to the ethnic group and other disease modifying factors such as sex and smoking. We cannot perform genotype-stratified analysis based on these factors, because the available data in these studies are discrete and do not allow for a meaningful stratified data synthesis. Fifth, we should also analyze the possibility of publication bias. Publication bias can result in the disappearance of some studies with negative results.

Clinical practice

We have assessed the pharmacogenetic data for predicting the efficacy and/or side effects of therapy. However, a huge barrier in translating these approaches into clinical application still remains. The cost effectiveness of these approaches needs to be carefully assessed. Further investigation into the importance of the genotype-differentiated response in airway reactivity in β2-AR polymorphism participants is still needed. The potential implication of the guidelines on asthma management will be the alternative treatment strategy. However, this approach will also require a formal prospective study to be undertaken before it is broadly recommended.

Summary

Polymorphism of the β2-AR is not a major risk factor for the development of asthma. Our results show that β2-AR polymorphism does not affect responses to LABA, ICS, or ICS plus LABA therapy. Future studies are highly needed to characterize all variations of genes and conduct comprehensive correlation studies.

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Disclosure of conflict of interest

None.

Abbreviations

β2-AR, β2-adrenergic receptor; FSC, fluticasone propionate/salmeterol; HWE, Hardy-Weinberg equilibrium; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; SABA, short-acting β-agonist.

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Checklist S1. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4-5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4-5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	15
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5-8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5-8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

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