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A meta-analysis: association between Beta-2 adrenergic receptor Arg16Gly polymorphism and asthma in China

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Abstract

For different populations, the association studies between the beta-2 adrenergic receptor (ADRB2) Arg16Gly mutation and asthma are conflict. This study was designated to evaluate ADRB2 Arg16Gly polymorphism and asthma in Chinese population. Systemic assessment was performed based on the data from PubMed, Embase, Web of Science, the Cochrane Library, and Chinese National Knowledge Infrastructure (CNKI) up to January 2019. Odds ratios (ORs) with their 95% confidence intervals (95% CIs) were calculated using STATA software. This meta-analysis included 6143 asthma patients and 5919 healthy persons from 34 studies. Overall, ADRB2 Arg16Gly polymorphism showed no significant influence on asthma in China. However, subgroup analyses according to geographic areas, age group and HWE in controls, only found a borderline significant effect for southern Chinese under the homozygotes genetic model (OR = 0.82, 95%CI = 0.68-1.00, P = 0.046). This meta-analysis suggests that ADRB2 Arg16Gly polymorphism is not be related to the development of asthma in China.

Keywords: ADRB2 Arg16Gly; polymorphism; asthma; meta-analysis; Chinese.

Practical Application: This meta-analysis proves that ADRB2 Arg16Gly polymorphism is not related to in development of asthma in China.

1 Introduction

Asthma is a kind of allergic disease of the respiratory tract, and has become a global public health problem in recent years (To et al., 2012). The prevalence of asthma is 0.2-21.0% wordwide, which is still increased, especially in developing countries such as China (To et al., 2012; Pearce et al., 2007; Yangzong et al., 2012). So far, numerous reports demonstrated that multiple genetic variations are involved in asthma. Among these genetic variations, the polymorphisms in beta-2 adrenergic receptor (ADRB2) have been most evaluated in asthma. For instance, single nucleotide polymorphisms of ADRB2 in the coding gene region including Arg16Gly (A46G, rs1042713), Gln27Glu (C79G, rs1042714), Thr164Ile (C491T, rs1800888) and Arg19Cys (T-47C, rs1042711) have proven the influence of ADRB2 activation on the small airways, suggesting the effective therapy of ADRB2 agonists in asthma (Pignatti 2004; Gao et al., 2004). Notably, the mutation of the Arg16Gly located at the ADRB2 gene has been extensively examined in studies on ADRB2 polymorphisms in asthma. The potential relationships on ADRB2 Arg16Gly polymorphism and asthma risk among Chinese people being remain conflicting. To our knowledge, it had lower statistical effect on the result than using a meta-analysis while the sample sizes in the individual studies are small. Therefore, this meta-analysis was performed to understand the importance of ADRB2 Arg16Gly polymorphism for asthma risk in Chinese population.

2 Materials and methods

2.1 Data collection

To evaluate the associations between ADRB2 Arg16Gly polymorphism and asthma risk, PubMed, Embase, Web of Science, the Cochrane Library, and Chinese National Knowledge Infrastructure (CNKI) prior to January 2019 were searched using terms: ("asthma" or "asthmatic") and ("beta-2 adrenergic receptor" or "ADRB2" or "b2-AR") and "polymorphism" and ("Chinese" or "China"). The search had no restriction in language or publication status.

Inclusion standards: (1) studies examining the relationship between ADRB2 Arg16Gly polymorphism and asthma, (2) study design with the case-control, (3) sufficient data of genotype frequency, (3) Chinese individuals. Exclusion standards: (1) overlapped literatures, (2) unextractable data, (3) not a case-control design, (4) abstract or reviews. The potentially relevant studies and extracted data from the identified publications, including first author's name, publication year, geographic areas, age group, sample size, and available genotype information from ADRB2 Arg16Gly polymorphism were screened by the investigators.

2.2 Statistical analysis

Data were analyzed by STATA version 12 (StataCorp LP, College Station, TX, USA). Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated and analyzed by Z-test. The model of G versus A, GG versus AA, GG versus (AA+AG) and (GG+AG) versus AA were examined with the asthma risk, respectively. Heterogeneity and Hardy-Weinberg equilibrium (HWE) were evaluated by I-squared based on Q and the df. When $P_{heterogeneity} < 0.1$ or $I^2 > 50\%$, a random-effects meta-analysis model was performed to estimate the pooled ORs; if not, a fixed-effects model was used. Pooled ORs were collected for the sensitivity assay. A p-value < 0.05 showed the significant change.

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3 Results

3.1 Characteristics of obtained reports

Through research, a total of 232 published articles assessing ADRB2 polymorphisms together with asthma were found. In total, 34 studies (Gao et al., 2000; Liao et al., 2001; Xing et al., 2001; Wang et al., 2001; Dai et al., 2002; Leung et al., 2003; Lin et al., 2003; Wang et al., 2004; Gao et al., 2004; Cui et al., 2007; Ye et al., 2011; Zhang et al., 2008; Yang et al., 2012; Feng et al., 2004; He et al., 2012; Xie et al., 2008; Liu et al., 2009; Shi & Zhou 2008; Tuerxun et al., 2007; Zheng et al., 2012; Fu et al., 2011; Qiu et al., 2010; Chan et al., 2008; Wang et al., 2009; Pan et al., 2005; Liu et al., 2006; Qiu & Yin 2008; Hua et al., 2008; Li et al., 2009; Chen et al., 2014; Liu et al., 2014; Hua et al., 2016; Tian et al., 2016; Guo et al., 2016) were used in this report, which met our inclusion criteria. The publication years between 2000 and 2016 were chosen for this meta-analysis. At the end, 6143 asthma cases and 5919 healthy controls for assessing the relation between ADRB2 Arg16Gly polymorphism and asthma risk among Chinese were included in this analysis study (Table 1).

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

References	Geographic areas	Age group	Case number	Control number	Cases			Controls			HWE	
					AA	AG	GG	AA	AG	GG	χ^2	*P*
Gao et al. (2000)	Beijing	Mixed	58	89	14	26	18	12	68	9	24.98	0.000
Liao et al. (2001)	Chongqing	Children	50	100	12	27	11	35	46	19	0.31	0.577
Xing et al. (2001)	Beijing	Adult	100	100	9	62	29	29	55	16	1.41	0.234
Wang et al. (2001)	Anhui	Adult	101	136	25	54	22	38	64	34	0.46	0.499
Dai et al. (2002)	Sichuan	Adult	87	94	33	33	21	36	33	25	7.80	0.005
Leung et al. (2003)	Hong Kong	Children	76	70	25	38	13	22	37	11	0.49	0.483
Lin et al. (2003)	Taiwan	Children	80	69	34	35	11	27	25	17	4.66	0.031
Wang et al. (2004)	Xinjiang	Adult	123	89	48	59	16	26	54	9	5.99	0.014
Gao et al. (2004)	Beijing	Adult	125	96	38	59	28	35	53	8	3.80	0.051
Cui et al. (2007)	Inner Mongolia	Adult	72	60	9	55	8	12	39	9	5.52	0.019
Ye et al. (2011)	Guizhou	Adult	31	37	5	19	7	5	26	6	6.11	0.013
Zhang et al. (2008)	Chongqing	Children	217	50	81	111	25	19	23	8	0.06	0.814
Yang et al. (2012)	Shanghai	Children	212	52	78	104	30	24	23	5	0.02	0.880
Feng et al. (2004)	Guizhou	Adult	74	39	13	35	26	6	28	5	7.44	0.006
He et al. (2012)	Guangdong	Adult	171	148	32	130	9	50	66	32	1.33	0.249
Xie et al. (2008)	Shanghai	Children	57	62	14	37	6	21	34	7	1.50	0.220
Liu et al. (2009)	Yunnan	Adult	120	120	27	59	34	23	71	26	4.07	0.044
Shi & Zhou (2008)	Shandong	Mixed	48	48	22	19	7	10	25	13	0.10	0.751
Tuerxun et al. (2007)	Xinjiang	Adult	76	89	13	36	27	26	54	9	5.99	0.014
Zheng et al. (2012)	Guangdong	Children	198	110	71	99	28	31	55	24	0.00	0.966
Fu et al. (2011)	Yunnan	Adult	238	265	85	88	65	106	92	67	22.33	0.000
Qiu et al. (2010)	Jiangsu	Adult	201	276	77	85	39	88	135	53	0.01	0.924
Chan et al. (2008)	Hong Kong	Children	295	173	101	135	59	51	89	33	0.28	0.597
Wang et al. (2009)	Taiwan	Children	442	510	138	207	97	173	250	87	0.04	0.837
Pan et al. (2005)	Jiangxi	Adult	45	45	10	21	14	6	34	5	11.79	0.001
Liu et al. (2006)	Inner Mongolia	Adult	42	30	6	34	2	6	20	4	3.45	0.063
Qiu & Yin (2008)	Jiangsu	Adult	70	112	25	31	14	34	55	23	0.01	0.930
Hua et al. (2008)	Shanghai	Children	96	96	43	38	15	23	50	23	0.17	0.683
Li et al. (2009)	Shanghai	Children	192	192	86	76	30	46	100	46	0.33	0.564
Chen et al. (2014)	Jiangsu	Adult	379	435	132	185	62	129	221	85	0.31	0.579
Liu et al. (2014)	Heilongjiang	Adult	429	483	150	209	70	153	237	93	0.01	0.943
Hua et al. (2016)	Shanghai	Children	1000	1000	396	448	156	308	500	192	0.19	0.666
Tian et al. (2016)	Jiangsu	Children	298	304	104	145	49	90	154	60	0.16	0.687
Guo et al. (2016)	Shandong	Children	340	340	84	218	38	116	184	40	6.60	0.010

3.2 Meta-analysis

The overall estimated ORs for all studies combined were 0.99, 0.96, 1.02, and 0.95 for contrast of allele (G vs. A), contrast of homozygotes (GG vs. AA), recessive (GG vs. AG+AA) and dominant models (GG+AG vs. AA), respectively (Table 2, Figure 1), these associations were not statistically significant (P>0.05). Next, we performed subgroup analyses according to geographic areas, age group and HWE in controls. Only a borderline significant effect for Southern Chinese was found under the homozygotes genetic model (OR = 0.82, 95%CI = 0.68-1.00, P = 0.046). There was no publication bias for the meta-analyses (t = 1.69, P=0.101; Figures 2 and 3). Sensitivity analysis in Table 2 indicated that the data used in this study were relatively stable and credible based on the fixed-effects model and the random-effects model.

4 Discussion

Many articles had been published to analyze the relation in ADRB2 Arg16Gly polymorphism and asthma, however, no

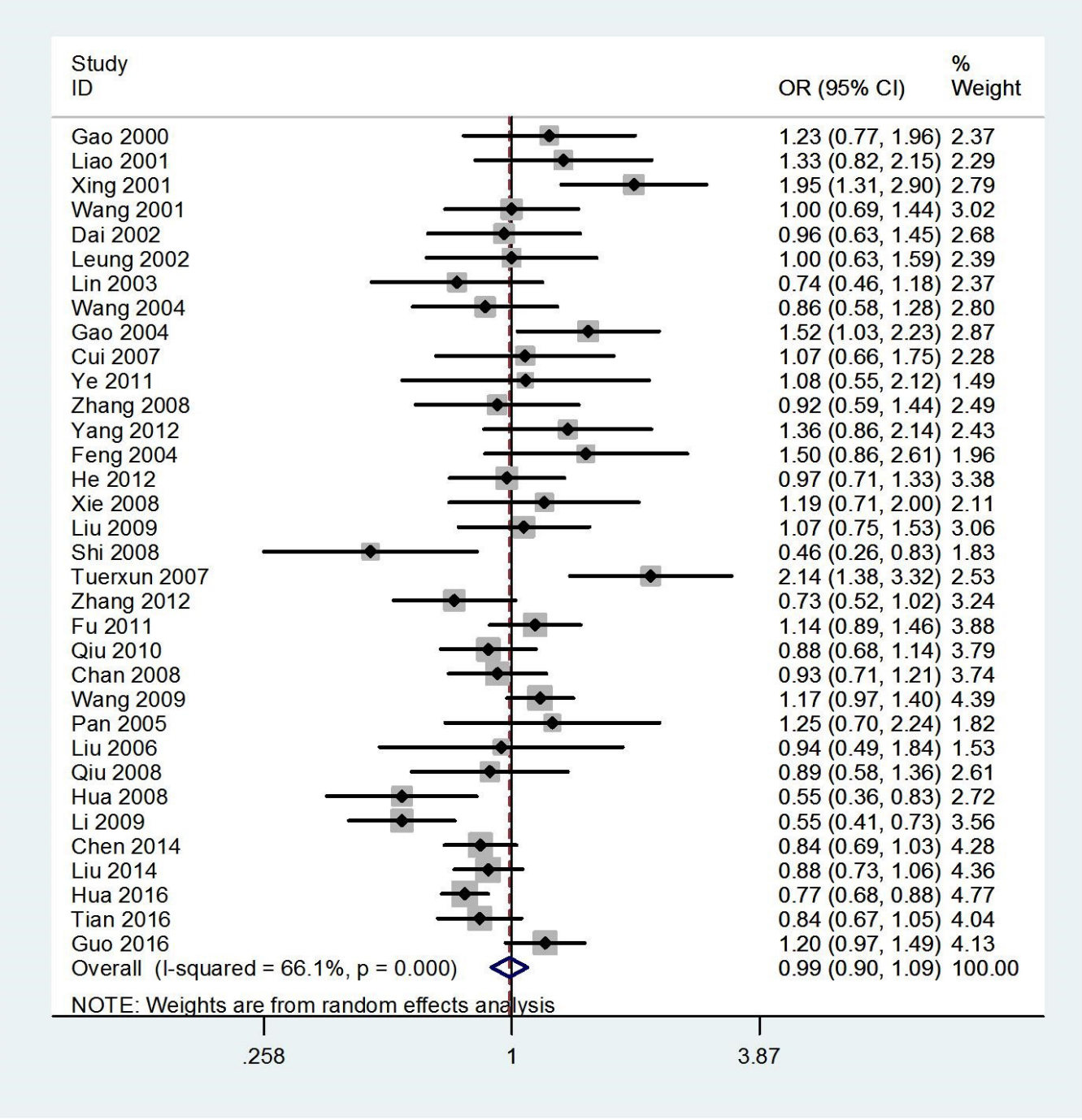

Figure 1. Forest plots of all selected studies regarding the association between ADRB2 Arg16Gly polymorphism and asthma risk within the Chinese population under the allele model.

Table 2. Association of the ADRB2 Arg16Gly polymorphism and asthma risk.

Analysis model		n	OR_r(95%CI)	OR_f(95%CI)	P_h
G vs. A	Total analysis	34	0.99 (0.90-1.09)	0.94 (0.90-0.99)	0.000
	North China	11	1.14 (0.92-1.40)	1.10 (0.99-1.22)	0.000
	South China	23	0.92 (0.90-1.02)	0.89 (0.84-0.95)	0.001
	Mixed	2	0.77 (0.29-1.99)	0.83 (0.58-1.20)	0.010
	Children	14	0.90 (0.77-1.04)	0.89 (0.83-0.95)	0.000
	Adult	18	1.08 (0.96-1.23)	1.02 (0.95-1.11)	0.004
	In HWE	22	0.92 (0.82-1.04)	0.89 (0.84-0.95)	0.000
GG vs. AA	Total analysis	34	0.96 (0.79-1.18)	0.89 (0.80-0.99)	0.000
	North China	11	1.41 (0.85-2.34)	1.23 (0.98-1.53)	0.000
	South China	23	0.82 (0.68-1.00)	0.80 (0.71-0.91)	0.006
	Mixed	2	0.66 (0.10-4.41)	0.69 (0.32-1.48)	0.019
	Children	14	0.80 (0.61-1.05)	0.79 (0.68-0.91)	0.001
	Adult	18	1.18 (0.88-1.59)	1.04 (0.88-1.22)	0.000
	In HWE	22	0.84 (0.66-1.07)	0.80 (0.71-0.91)	0.000
GG vs. AG+AA	Total analysis	34	1.02 (0.86-1.23)	0.97 (0.88-1.06)	0.000
	North China	11	1.33 (0.86-2.05)	1.19 (0.98-1.44)	0.000
	South China	23	0.92 (0.76-1.10)	0.90 (0.81-1.01)	0.000
	Mixed	2	1.38 (0.17-11.48)	1.54 (0.83-2.87)	0.002
	Children	14	0.86 (0.72-1.03)	0.87 (0.76-0.99)	0.135
	Adult	18	1.19 (0.88-1.60)	1.05 (0.92-1.22)	0.000
	In HWE	22	0.87 (0.72-1.05)	0.87 (0.79-0.97)	0.000
GG+AG vs. AA	Total analysis	34	0.95 (0.81-1.11)	0.90 (0.83-0.97)-	0.000
	North China	11	1.14 (0.81-1.61)	1.12 (0.95-1.31)	0.000
	South China	23	0.88 (0.74-1.03)	0.84 (0.76-0.92)	0.000
	Mixed	2	0.39 (0.21-1.73)	0.36 (0.21-1.74)	0.473
	Children	14	0.88 (0.70-1.12)	0.84 (0.76-0.93)	0.000
	Adult	18	1.08 (0.81-1.11)	1.01 (0.90-1.14)	0.002
	In HWE	22	0.93 (0.77-1.12)	0.85 (0.78-0.93)	0.000

ORr: Odd ratio for random-effect model; ORf: Odd ratio for fixed-effect model; P_h *P* value for heterogeneity test.

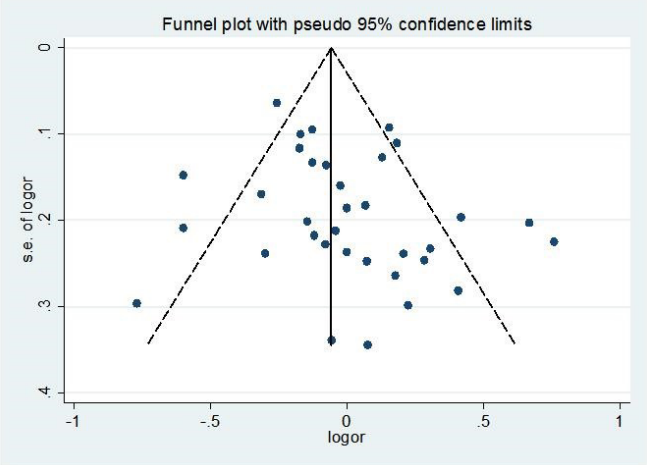

Figure 2. Publication bias assessment of ADRB2 Arg16Gly polymorphism and asthma risk with Begg's funnel plot.

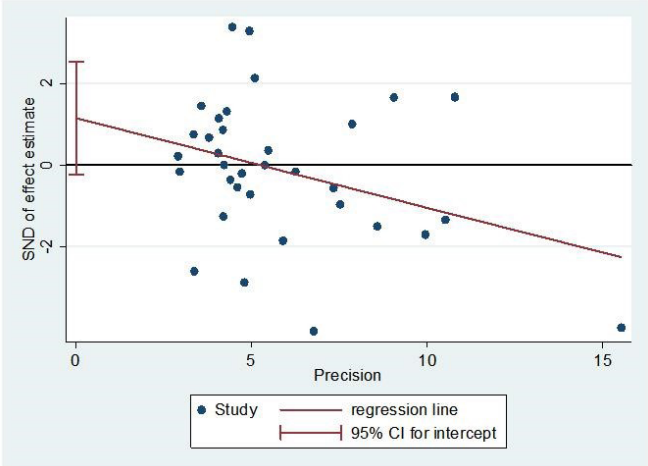

Figure 3. Egger's linear regression for the Begg's funnel plot.

comprehensive exact conclusion was obtained. In a previous study, ADRB2 Arg/Gly16 showed a significant association with asthma in Asian population (Xie et al., 2014). The subgroup analysis based on the age showed that, compared to the other genotypes, Gly16 had recessive protective functions for children (Thakkinstian et al., 2005). Individual study could generate diverse results as the variability in region and individual in different populations, or due to the limit of cases. Furthermore, a unique culture and lifestyle from diverse ethnic group resulted in the different genetic trait. To avoid these limits, we performed this study to further survey the relation about ADRB2 Arg16Gly polymorphism and asthma in Chinese populations.

Analyses of 34 publications including 6143 asthma cases and 5919 healthy controls provided the evidence that ADRB2 Arg16Gly polymorphism was not an important risk factor for asthma in Chinese. Subgroup analysis suggested that only a borderline significant effect for southern Chinese was found under the homozygotes genetic model. No association between ADRB2 Arg16Gly polymorphism and the risk of asthma was found in other subgroups. Therefore, this meta-analysis indicated that there may be no connection between ADRB2 Arg16Gly polymorphism and asthma in China. These findings were also found in other meta-analyses, which showed that ADRB2 Arg16Gly gene polymorphism was not related to asthma in the children and general populations (Guo et al, 2016; Liang et al., 2014; Khan et al., 2018).

Most importantly, ADRB2 Arg16Gly polymorphism may vary greatly between different races, but this study mainly focused on Chinese population. In the meta-analysis, heterogeneity is often observed among genetic association studies. Although subgroup analysis was done according to geographic areas, ages and HWE in controls, the heterogeneity was not effectively decreased. Therefore, other factors may be the potential reasons for their heterogeneity. Additionally, the following deficiencies need to be mentioned: First, significant heterogeneity still existed in the subgroup analysis, thus might introduce some bias. Secondly, we cannot perform some other subgroup analyses such as sex, and asthma phenotype due to the limitation of data. Thirdly, the risks for asthma are multifactorial and complicated, and only genetic variation is often difficult to determine the cause-effect relationships of asthma.

5 Conclusion

This meta-analysis proves that ADRB2 Arg16Gly polymorphism is not related to in development of asthma in China. However, due to some limitations exited in this study, further studies are needed to validate the interactions between ADRB2 Arg16Gly polymorphism and asthma susceptibility based on more information.

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