**Correspondence**

**Comments on ‘Association of FcRIβ polymorphisms with risk of asthma and allergic rhinitis: evidence based on 29 case–control studies’**

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Guo et al. (Bioscience Reports (2018) 38, BSR20180177) published a meta-analysis concerning the association between five single nucleotide polymorphisms (SNPs) in the high-affinity IgE receptor β chain (FcεRIβ) gene, namely E237G, -109 C/T, Rsal_in2, Rsal_ex7, and I181L, and risk of asthma and allergic rhinitis based on available 29 case–control studies. Summary odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of association of SNPs in FcεRIβ gene with allergic diseases risk. They found that FcεRIβ E237G (237G vs. 237E: OR = 1.28, 95% CI = 1.06–1.53) and -109 C/T (TT vs. CT+CC: OR = 1.58, 95% CI = 1.26–1.98) were risk factors for allergic diseases. Guo et al.’s findings are interesting, but we found that several issues should be clarified after carefully reading the paper. Here, we intended to comment on these data clarifications.

Dear editor,

We researched the relevant studies about the association between the high-affinity IgE receptor β chain (FcεRIβ) polymorphisms and allergic diseases risk in Medline, Embase, Web of Science, Chinese National Knowledge Infrastructure, and Wanfang databases. No limit of start year and month was set, and the updated time was August 2019. The terms, search strategies, and inclusion/exclusion criteria were the same as reported by Guo et al. [1]. Comparing our retrieved studies with the ones in Table 1 of Guo et al.’s paper [1], it seems that some errors or mistakes should be corrected.

First, several relevant studies that met the inclusion criteria were missed in Guo et al.’s paper [2–15]. Of the 14 missed studies, 5 articles were published before January 2000 [2–6], which was the start time of published paper restricted in Guo et al.’s literature searching strategy [1]; 3 reports were from Japan [2,6,11], 4 studies were from China [9,13–15], 1 each was from South Africa [3], Switzerland [4], Australia [5], India [7], South Korea [8], the U.S.A. [11], and Hungary [12], respectively. In Green et al.’s study, black and white populations were recruited, respectively [3]. In Undarmaa et al.’s report, children and adult populations were recruited, respectively [10].

Second, several studies published by the same research group were included in Guo et al.’s report [1]. According to the inclusion and exclusion criteria, when more than two studies were reported by the same research group, only the paper with the largest sample size was included in the analysis. We think Cui et al.’s study [16], published in 2004, with 106 adult asthmatics and 106 controls, were incorporated into their another paper, published in 2003, with 216 (number including adults and children) cases and 198 controls [17]. Similarly, the study populations in Hua et al.’s papers [18,19] and the Chinese Han case/control populations in Ramphul et al.’s article [20], were recruited by the same research group, the two smaller sample-size studies should be excluded from the analysis [18,20].
Table 1 Main characteristics of eligible studies

| Author          | Year | Country  | Ethnicity | Atopy     | Sample size (n) | Genotype frequency (n) | HWE (P) |
|-----------------|------|----------|-----------|-----------|------------------|------------------------|---------|
|                  |      |          |           |           | Case Control EE  | Case Control EG  |       |
|                  |      |          |           |           | Case Control GG  | Case Control GG        |         |
|                  |      |          |           |           |                  |                        |         |
|                  |      |          |           |           |                  |                        |         |
| **FcεRIβ gene E237G polymorphism** |      |          |           |           |                  |                        |         |
| Shirakawa       | 1996 | Japan    | Asian     | asthma    | 300 100          | 256 44 0              | 94 6 0   | 1.000 |
|                  |      |          |           |           |                  |                        |         |
| Green           | 1998 | South Africa | African  | asthma    | 41 42           | 27 12 2              | 25 17 0  | 0.172 |
| Green           | 1998 | South Africa | Caucasian | asthma    | 46 51           | 35 11 0              | 47 4 0   | 1.000 |
| Rohrbach        | 1998 | Switzerland | Caucasian | asthma    | 224 159         | 207 17 0             | 151 8 0  | 1.000 |
| Ishizawa        | 1999 | Japan     | Asian     | asthma    | 90 102          | 70 19 1              | 81 21 0  | 0.593 |
| Chen            | 2000 | China     | Asian     | asthma    | 101 47          | 59 39 3              | 30 16 1  | 1.000 |
| Soriano         | 2000 | Spain     | Caucasian | asthma    | 145 47          | 134 11 0             | 43 4 0   | 1.000 |
| Takabayashi     | 2000 | Japan     | Asian     | asthma    | 100 100         | 69 27 4              | 65 33 2  | 1.000 |
| Green           | 1998 | South Africa | Caucasian | asthma    | 36 51           | 24 35 2              | 41 16 1  | 0.001 |
| Green           | 2000 | China     | African   | asthma    | 101 47          | 59 39 3              | 30 16 1  | 1.000 |
| Soriano         | 2000 | Spain     | Caucasian | asthma    | 145 47          | 134 11 0             | 43 4 0   | 1.000 |
| Zeng            | 2001 | China     | Asian     | asthma    | 219 198         | 125 80 11            | 148 46 4 | 0.766 |
| Korzycka        | 2004 | Poland    | Caucasian | asthma    | 98 87           | 92 6 0               | 83 4 0   | 1.000 |
| Rigoli          | 2004 | Italy     | Caucasian | asthma    | 100 103         | 79 16 5              | 102 1 0  | 1.000 |
| Shahra          | 2004 | India     | Asian     | asthma    | 329 266         | 300 29 0             | 250 16 0 | 1.000 |
| Zhang (Chinese) | 2004 | Singapore | Asian     | asthma    | 141 157         | 81 57 3              | 108 42 7 | 1.194 |
| Zhang (Indian)  | 2004 | Singapore | Asian     | asthma    | 82 98           | 71 10 1              | 80 18 0  | 1.000 |
| Zhang (Malay)   | 2004 | Singapore | Asian     | asthma    | 68 100          | 49 19 0              | 77 23 0  | 0.353 |
| Zhao            | 2004 | China     | Asian     | asthma    | 151 105         | 126 23 2             | 92 13 0  | 1.000 |
| Kim             | 2006 | Korea     | Asian     | asthma    | 307 264         | 235 64 8             | 177 81 6 | 0.353 |
| Li              | 2006 | China     | Asian     | asthma    | 50 40           | 43 7 0               | 40 0 0   | 1.000 |
| Liu             | 2006 | China     | Asian     | asthma    | 60 50           | 45 14 1              | 39 10 1  | 0.527 |
| Kim             | 2009 | Korea     | Asian     | asthma    | 347 303         | 244 99 4             | 217 81 5 | 0.409 |
| Wang            | 2009 | China     | Asian     | asthma    | 446 506         | 309 121 16           | 314 165 27| 0.396 |
| Undarmaa        | 2010 | Japan     | Asian     | asthma    | 367 630         | 256 102 9            | 440 165 25| 0.061 |
| Undarmaa        | 2010 | Japan     | Asian     | asthma    | 322 336         | 243 70 9             | 242 85 9 | 0.642 |
| Murk            | 2011 | U.S.A. mixed| asthma    | asthma    | 100 486         | 91 9 0               | 452 33 1 | 0.470 |
| Dmitrieva       | 2012 | Russia    | Caucasian | asthma    | 224 172         | 217 7 0              | 170 2 0  | 1.000 |
| Ungvari         | 2012 | Hungary   | Caucasian | asthma    | 436 785         | 418 17 1             | 723 38 4 | 0.004 |
| Zheng           | 2012 | China     | Asian     | asthma    | 198 110         | 126 61 11            | 76 29 5 | 0.325 |
| Chen            | 2014 | China     | Asian     | asthma    | 46 52           | 38 6 2               | 38 6 8  | <0.001 |
| Lan             | 2014 | China     | Asian     | asthma    | 58 50           | 41 16 1              | 47 3 0   | 1.000 |
| Ramphul         | 2014 | India     | Asian     | asthma    | 192 188         | 170 21 1             | 163 24 1 | 0.605 |
| Amo             | 2016 | Spain     | Caucasian | rhinitis  | 366 526         | 330 36 0             | 487 39 0 | 1.000 |
| Amo             | 2016 | Spain     | Caucasian | asthma    | 149 526         | 146 3 0              | 487 39 0 | 1.000 |
| Hua             | 2016 | China     | Asian     | asthma    | 1000 1000       | 659 276 65           | 688 289 23| 0.252 |
| Yang            | 2017 | China     | Asian     | asthma    | 74 110          | 38 31 5              | 77 30 3  | 1.000 |

**FcεRIβ gene C-109T polymorphism**

| Author          | Year | Country  | Ethnicity | Atopy     | Sample size (n) | Genotype frequency (n) | HWE (P) |
|-----------------|------|----------|-----------|-----------|------------------|------------------------|---------|
|                  |      |          |           |           |                  |                        |         |
| **case control**|      |          |           |           | CC | CT | TT | CC | CT | TT |         |

Dickson 1999 Australia Caucasian asthma 44 26 11 17 16 6 15 5 0.428

Cui 2003 China Asian asthma 216 198 23 106 87 19 103 76 0.059

Gan 2004 China Asian asthma 45 45 10 12 23 12 14 19 0.015

Zhao 2004 China Asian asthma 126 87 11 69 46 9 38 40 0.996

Hizawa 2006 Japan Asian asthma 374 374 39 178 157 49 169 156 0.762

Continued over
Table 1 Main characteristics of eligible studies (Continued)

| Author | Year | Country | Ethnicity | Atopy | Sample size (n) | Genotype frequency (n) |
|--------|------|---------|-----------|-------|----------------|-----------------------|
|        |      |         |           |       | case control   | CC | CT | TT | CC | CT | TT | HWE (P) |
| Kim    | 2006 | Korea   | Asian     | asthma| 302 | 264 | 17 | 139 | 146 | 23 | 128 | 113 | 0.114   |
| Potaczek| 2007 | Poland  | Caucasian | asthma| 154 | 154 | 25 | 72  | 57  | 27 | 70  | 57  | 0.495   |
| Kim    | 2009 | Korea   | Asian     | asthma| 346 | 303 | 20 | 167 | 159 | 28 | 135 | 140 | 0.576   |
| Sharma | 2009 | India   | Asian     | asthma| 237 | 221 | 89 | 108 | 40  | 34 | 118 | 69  | 0.156   |
| Tikhonova| 2010| Russia  | Caucasian | asthma| 140 | 136 | 18 | 69  | 57  | 27 | 70  | 48  | 0.339   |
| Ramphul| 2014 | India   | Asian     | asthma| 189 | 188 | 55 | 99  | 35  | 28 | 66  | 35  | 0.505   |
| Wan    | 2014 | China   | Asian     | asthma| 58  | 50  | 2  | 25  | 31  | 1  | 16  | 33  | 1.000   |
| Amo    | 2016 | Spain   | Caucasian | rhinitis| 366 | 526 | 78 | 188 | 100 | 105| 277 | 144 | 0.176   |
| Amo    | 2016 | Spain   | Caucasian | rhinitis| 149 | 526 | 35 | 67  | 47  | 105| 277 | 144 | 0.176   |
| Hua    | 2016 | China   | Asian     | asthma| 1000| 1000| 148| 436 | 416 | 124| 470 | 406 | 0.502   |

Abbreviation: HWE, Hardy–Weinberg equilibrium.

Table 2 Summary ORs for the association between FcεRIβ C-109T polymorphism and allergic diseases risk

| Comparisons | Sample size | Number of studies | Hypothesis tests | Heterogeneity tests | Publication bias test (P) |
|-------------|-------------|-------------------|------------------|---------------------|-------------------------|
|             | Case/control | OR (95% CI) | z | P | $\chi^2$ (df) | P | I² (%) | Begg’s test | Egger’s test |
| Overall     | 7492/7144 | 14 | 1.024 (0.900–1.164) | 0.36 | 0.722 | 37.83 (13) | <0.001 | 65.6 | 0.784 | 0.958 |
| C vs. T     | 1994/1862 | 14 | 1.007 (0.759–1.335) | 0.05 | 0.963 | 36.77 (13) | <0.001 | 64.6 | 0.870 | 0.582 |
| CC vs. CT   | 2333/2231 | 14 | 1.028 (0.807–1.311) | 0.22 | 0.823 | 30.59 (13) | 0.004 | 57.5 | 0.702 | 0.419 |
| CT vs. TT   | 3165/3051 | 14 | 0.984 (0.890–1.089) | 0.31 | 0.758 | 14.33 (13) | 0.351 | 9.3 | 0.547 | 0.538 |
| CC+CT vs. TT| 3746/3572 | 14 | 1.01 (0.909–1.102) | 0.01 | 0.989 | 21.72 (13) | 0.060 | 40.1 | 0.784 | 0.670 |
| CC vs. CT+TT| 3746/3572 | 14 | 1.015 (0.788–1.307) | 0.11 | 0.911 | 37.20 (13) | <0.001 | 65.1 | 0.956 | 0.446 |

Stratification by ethnicity

|             | Sample size | Number of studies | Hypothesis tests | Heterogeneity tests | Publication bias test (P) |
|-------------|-------------|-------------------|------------------|---------------------|-------------------------|
|             | Case/control | OR (95% CI) | z | P | $\chi^2$ (df) | P | I² (%) | Begg’s test | Egger’s test |
| Asians      | 5786/5460 | 10 | 1.052 (0.883–1.254) | 0.57 | 0.567 | 36.51 (9) | <0.001 | 75.3 | 0.655 | 0.802 |
| CC+CT vs. TT| 2893/2730 | 10 | 1.070 (0.895–1.280) | 0.74 | 0.458 | 18.97 (9) | 0.025 | 52.6 | 0.325 | 0.304 |
| CC vs. CT+TT| 2893/2730 | 10 | 0.998 (0.895–1.434) | 0.01 | 0.992 | 36.70 (9) | <0.001 | 75.5 | 0.788 | 0.537 |
| Caucasians  | 1706/1684 | 4 | 0.984 (0.858–1.127) | 0.24 | 0.813 | 0.89 (3) | 0.828 | <0.1 | 0.042 | 0.036 |
| CC+CT vs. TT| 853/842 | 4 | 0.919 (0.747–1.130) | 0.80 | 0.422 | 1.99 (3) | 0.576 | <0.1 | 0.174 | 0.201 |
| CC vs. CT+TT| 853/842 | 4 | 1.067 (0.836–1.362) | 0.52 | 0.601 | 0.48 (3) | 0.924 | <0.1 | 1.000 | 0.412 |

Stratification by atopic disease categories

|             | Sample size | Number of studies | Hypothesis tests | Heterogeneity tests | Publication bias test (P) |
|-------------|-------------|-------------------|------------------|---------------------|-------------------------|
|             | Case/control | OR (95% CI) | z | P | $\chi^2$ (df) | P | I² (%) | Begg’s test | Egger’s test |
| Asthma      | 6462/6092 | 13 | 1.024 (0.885–1.185) | 0.32 | 0.750 | 37.83 (12) | <0.001 | 68.3 | 0.903 | 0.950 |
| CC+CT vs. TT| 3231/3048 | 13 | 1.032 (0.883–1.207) | 0.40 | 0.691 | 21.52 (12) | 0.043 | 44.2 | 1.000 | 0.712 |
| CC vs. CT+TT| 3231/3048 | 13 | 0.997 (0.744–1.338) | 0.02 | 0.983 | 37.13 (12) | <0.001 | 67.7 | 0.542 | 0.472 |

Stratification by HWE

|             | Sample size | Number of studies | Hypothesis tests | Heterogeneity tests | Publication bias test (P) |
|-------------|-------------|-------------------|------------------|---------------------|-------------------------|
|             | Case/control | OR (95% CI) | z | P | $\chi^2$ (df) | P | I² (%) | Begg’s test | Egger’s test |
| C vs. T     | 7402/7054 | 13 | 1.035 (0.907–1.180) | 0.51 | 0.613 | 36.83 (12) | <0.001 | 67.4 | 1.000 | 0.861 |
| CC+CT vs. TT| 3701/3527 | 13 | 1.006 (0.913–1.108) | 0.11 | 0.911 | 21.00 (12) | 0.050 | 42.9 | 0.272 | 0.483 |
| CC vs. CT+TT| 3701/3527 | 13 | 1.026 (0.789–1.335) | 0.19 | 0.848 | 36.76 (12) | <0.001 | 67.4 | 0.807 | 0.516 |

Abbreviation: df, degree of freedom.
Figure 1. Forest plots for the association of FcεRIβ E237G polymorphism with allergic diseases risk (subgroup analysis by HWE)

Third, one study reported by Laprise et al. [21], with atopic/non-atopic contrast groups, not all the subjects in atopic group met with the diagnosis criteria of asthma, should be excluded from the analysis.

Fourth, the reported genotype frequency for the C-109T or E+237G polymorphisms of FcεRIβ gene in two studies of Guo et al.'s paper [1] were not in agreement with the ones in their original papers [22,23]. In Sharma and Ghosh's study, the CC, CT, and TT genotype frequency for C-109T polymorphism in case/control groups were (89, 108, and 40)/(34, 118, and 69), respectively [22], which were wrongly counted as (87, 113, and 37)/(39, 108, and 74), respectively, in Guo et al.'s paper [1]. In Amo et al.'s published article, the EE, EG, and GG genotype frequency in control group for E+237G polymorphism were 487, 39, and 0, respectively [23], which were wrongly counted as 144, 277, and 105, respectively [1].

Considering the above-listed mistakes or errors in Guo et al.'s published paper, it seems that the findings and conclusions of Guo et al.'s study were not entirely reliable [1]. To overcome the limitations, we performed an updated meta-analysis to re-assess the associations of C-109T and E+237G polymorphisms in the FcεRIβ gene with allergic
Figure 2. Forest plot for the association of FcεRIβ E237G polymorphism with allergic diseases risk (subgroup analysis by ethnicity)

disease (asthma and allergic rhinitis) risk. The statistical analysis methods and software used in this comment were the same as reported by Guo et al., unless otherwise indicated [1].

The main characteristics of the eligible studies [2–17,19,20,22–42], including the first author, publication year, country where individual study was conducted, ethnicity of study population, atopic disease category, sample size of case/control groups, the detailed genotype frequency, and the $P$-values for Hardy–Weinberg Equilibrium (HWE) test, were shown in Table 1. There were 36 case–control studies about the association between E+237G variant and allergic diseases risk [2–4,6–15,17,19,20,23–28,30–33,36,38,39,41,42], and 15 were about the correlation of C-109T polymorphism with allergic diseases risk [5,8,12,14,17,19,22,23,29,34,35,37,38,40]. Of the 15 case–control studies about C-109T polymorphism and allergic disease risk (14 ones according to ethnicity or HWE classification), 10
Figure 3. Forest plot for the association of FcεRIβ E237G polymorphism with allergic diseases risk (subgroup analysis by allergy category)

were performed in Asians [8,14,17,19,20,22,29,34,35,38] and 4 were conducted in Caucasians [5,23,37,40], respectively; 13 studies were about asthma risk [5,8,17,19,20,22,29,34,37,38,40], 1 was about allergic rhinitis risk [23], and 1 about asthma and rhinitis risk [23], respectively; genotype frequency distribution in control groups of 13 studies were in agreement with HWE [5,8,17,19,20,22,29,34,35,37,38,40] and 1 was not [29], respectively. Of the 36 case–control studies about E+237G variant with allergic diseases risk (35 ones according to ethnicity or HWE classification), 25 were carried out in Asians [2,6–10,13–15,17,19,20,24–26,28,29,31–33,36,38,39,42], 8 were performed in Caucasians [3,4,12,23,30,31,41], 1 in Africans [3] and 1 in mixed populations [11], respectively; 31 studies were about asthma risk [2–4,6–15,17,19,20,24–26,28,29,31–33,36,38,39,41,42], 2 were on rhinitis risk [23,27], and 3 were concerned with asthma/rhinitis risk [23,30,31], respectively; genotype frequency distribution in control groups of 32 studies were in line with HWE [2–4,6–11,13–15,17,19,20,23–26,28–33,36,38,39,41,42] and 3 were not [12,13,27], respectively.
Figure 4. Forest plot of cumulative meta-analysis for the association of FcεRIβ E237G polymorphism with allergic diseases risk.

Table 2 listed the summary odds ratios (ORs) of the association of FcεRIβ C-109T polymorphism with allergic diseases risk. Overall, no significant associations between C-109T polymorphism and allergic diseases risk were observed (OR = 1.001, 95% confidence interval (CI): 0.909–1.102 for CC+CT vs. TT and OR = 1.015, 95% CI: 0.788–1.307 for CC vs. CT+TT, respectively). When subgroup analyses by ethnicity (Asian and Caucasian), allergic disease classification (asthma, rhinitis, and both) and HWE (in and not) were performed, we did not find any statistically significant associations of C-108T polymorphism with allergic diseases risk (Table 2). No any publication and other small study related biases were observed in overall and subgroup analyses (Table 2).

Table 3 showed the summary ORs for the association between FcεRIβ E237G variant and allergic diseases risk. Overall, we observed FcεRIβ 237G allele was associated with increased risk of allergic diseases in total population (OR = 1.178, 95% CI: 1.022–1.357 for G vs. E and OR = 1.207, 95% CI: 1.031–1.411 for GG+EG vs. EE, respectively) (Table 3 and Figure 1). When restricted the analysis to the studies with control groups’ genotype frequency distribution were met with HWE, we observed an elevated risk of allergic diseases among subjects carrying EG or GG genotypes, in comparison with EE genotype carriers (OR = 1.225, 95% CI: 1.041–1.442) (Table 3 and Figure 1). When stratified analyses were conducted by ethnicity, we found an increased risk of allergic diseases in subjects carrying EG or GG genotypes.
Figure 5. Sensitivity analysis for the association between $F_{c}:RI\beta$ E237G polymorphism and allergic diseases risk

Figure 6. Egger's funnel plots for the association between $F_{c}:RI\beta$ E237G polymorphism and allergic diseases risk

(A) G allele vs. E allele; (B) EG/GG genotypes vs. EE genotype.
Table 3 Summary ORs for the association between FcεRIβ E273G polymorphism and allergic diseases risk

| Comparisons                        | Sample size | Number of studies | Hypothesis tests | Heterogeneity tests | Publication bias test (P) |
|-------------------------------------|-------------|-------------------|------------------|---------------------|--------------------------|
|                                     |             |                   | OR (95% CI)      | Z       | P       | χ² (df) | P    | I² (%) | Begg’s test | Egger’s test |             |
| Overall                             |             |                   |                  |         |         |         |      |       |          |            |             |
| G vs. E                             | 14552/14956 | 35                | 1.178 (1.022–1.357) | 2.25   | 0.024  | 84.83 (34) | <0.001 | 59.9    | 0.028 | 0.025        |
| GG+GE vs. EE                        | 7276/7478   | 35                | 1.207 (1.031–1.411) | 2.35   | 0.019  | 82.95 (34) | <0.001 | 59.0    | 0.024 | 0.008        |
| Stratification by ethnicity         |             |                   |                  |         |         |         |      |       |          |            |             |
| Asians                              |             |                   |                  |         |         |         |      |       |          |            |             |
| G vs. E                             | 10694/10080 | 25               | 1.158 (0.994–1.350) | 1.88   | 0.060  | 65.83 (24) | <0.001 | 63.5    | 0.176 | 0.122        |
| GG+GE vs. EE                        | 5347/5040   | 25               | 1.189 (1.001–1.412) | 1.98   | 0.048  | 64.41 (24) | <0.001 | 62.7    | 0.148 | 0.046        |
| Caucasians                          |             |                   |                  |         |         |         |      |       |          |            |             |
| G vs. E                             | 3576/3820   | 8                | 1.544 (0.884–2.697) | 1.53   | 0.126  | 19.63 (7) | 0.006  | 64.3    | 0.026 | 0.028        |
| GG+GE vs. EE                        | 1788/1910   | 8                | 1.547 (0.895–2.673) | 1.56   | 0.118  | 18.02 (7) | 0.012  | 61.1    | 0.026 | 0.028        |
| Stratification by atopic disease categories |             |                   |                  |         |         |         |      |       |          |            |             |
| Asthma                              |             |                   |                  |         |         |         |      |       |          |            |             |
| G vs. E                             | 12660/13324 | 31               | 1.148 (0.994–1.326) | 1.88   | 0.060  | 72.22 (30) | <0.001 | 58.5    | 0.051 | 0.081        |
| GG+GE vs. EE                        | 6330/6662   | 31               | 1.164 (0.994–1.364) | 1.89   | 0.059  | 69.11 (30) | <0.001 | 56.6    | 0.047 | 0.031        |
| Allergic rhinitis                   |             |                   |                  |         |         |         |      |       |          |            |             |
| G vs. E                             | 764/1252    | 2                | 0.680 (0.124–3.737) | 0.44   | 0.657  | 7.30 (1)   | 0.007  | 86.3    | 0.317 | -            |
| GG+GE vs. EE                        | 382/626     | 2                | 0.740 (0.103–5.324) | 0.30   | 0.765  | 9.20 (1)   | 0.002  | 89.1    | 0.317 | -            |
| Asthma and/or allergic rhinitis     |             |                   |                  |         |         |         |      |       |          |            |             |
| G vs. E                             | 1128/1432   | 3                | 2.955 (0.616–14.181) | 1.35   | 0.176  | 10.60 (2) | 0.005  | 81.1    | 0.117 | 0.449        |
| GG+GE vs. EE                        | 564/716     | 3                | 2.796 (0.646–12.109) | 1.37   | 0.169  | 9.01 (2)   | 0.011  | 77.8    | 0.117 | 0.451        |
| Stratification by HWE               |             |                   |                  |         |         |         |      |       |          |            |             |
| Yes                                 |             |                   |                  |         |         |         |      |       |          |            |             |
| G vs. E                             | 13122/13122 | 32               | 1.211 (1.046–1.403) | 2.55   | 0.011  | 76.29 (31) | <0.001 | 59.4    | 0.009 | 0.008        |
| GG+GE vs. EE                        | 6561/6581   | 32               | 1.225 (1.041–1.442) | 2.44   | 0.015  | 75.76 (31) | <0.001 | 59.1    | 0.011 | 0.004        |

Abbreviation: df, degree of freedom.
cumulative meta-analysis also indicated that there was high heterogeneity of the results of the included individual studies.

Sensitivity analysis was performed by sequentially omitting each individual study in the order of publication year and the pooled ORs were estimated repeatedly, which was used to evaluate the stability of the results of present meta-analysis. The sensitivity analysis showed that the association of EG and GG genotypes with increased risk of allergic diseases maintained statistically significant when removing any each individual study (Figure 5). Egger’s regression test and Begg’s rank correlation test were used to evaluate the small-study effects and potential publication bias in current meta-analysis. Both tests indicated that the significant association of G allele or EG+GG genotypes with elevated risk of allergic diseases might strongly influenced by small-study effect or publication bias (Table 3). The Egger’s funnel plots for the association between E237G polymorphism and allergic diseases risk also showed that the OR distributions for both G allele vs. E allele (Figure 6A) and EG+GG vs.EE (Figure 6B) were obviously asymmetrical.

There are some inherent limitations of meta-analysis which should be taken into consideration when using the results of this comment. First, there was high heterogeneity in this meta-analysis, especially in the case of association of E237G variant with allergic diseases risk. Although, subgroup analyses were performed on the basis of ethnicity, allergic disease category and HWE, heterogeneity among the included studies still be statistically significant in all subgroups. Second, publication bias tests indicated that the probable existence of publication bias, i.e. some unpublished negative results studies thus could not be included in this analyses might result in an over-estimated association of E237G with allergic disease risk.

In conclusion, the results of Guo et al.’s study [1] should be interpreted with caution. To make an asserted conclusion, well-designed studies with large number of homogeneous population are required. We do hope that this comment will be helpful to clarify the results presented by Guo et al. [1].

Competing Interests
The authors declare that there are no competing interests associated with the manuscript.

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Author Contribution
H.Y.: designed the study, performed the statistical analysis and edited the manuscript. L.Z.: conducted literature search and extracted data from individual studies. Y.Z. and M.Y.: prepared and reviewed the manuscript. S.W.: conducted literature search and data checking. All authors approved the final manuscript.

Abbreviations
CI, confidence interval; FcεRIβ, high-affinity IgE receptor β chain; HWE, Hardy–Weinberg equilibrium; OR, odds ratio.

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