Association between ADAM metallopeptidase domain 33 gene polymorphism and risk of childhood asthma: a meta-analysis

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Abstract

This study aimed to investigate the association between ADAM metallopeptidase domain 33 (ADAM33) gene polymorphisms and the risk of childhood asthma. The relevant studies about the relationship between ADAM33 gene polymorphisms and childhood asthma were searched from electronic databases and the deadline of retrieval was May 2016. The single nucleotide polymorphisms (SNPs) of ADAM33 (rs511898, rs2280092, rs3918396, rs528557, rs2853209, rs44707, rs2280091 and rs2280089) were analyzed based on several models including the allele, codominant, recessive and dominant models. The results showed that the ADAM33 rs2280091 polymorphism in all four genetic models was associated with an increased risk of childhood asthma. Positive associations were also found between the polymorphisms rs2280090, rs2787094, rs44707 and rs528557 and childhood asthma in some genetic models. This meta-analysis suggested that ADAM33 polymorphisms rs2280091, rs2280090, rs2787094, rs44707 and rs528557 were significantly associated with a high risk of childhood asthma.

Key words: Childhood; Asthma; ADAM33; Gene polymorphisms; Asthma risk; Meta-analysis

Introduction

Asthma is a common respiratory disorder in both adults and children, characterized by bronchial hyper-responsiveness, airway inflammation, airflow obstruction, wheezing and breathlessness. Nowadays, the prevalence of asthma in children is increasing worldwide and has become one of the major causes of child hospitalization and morbidity (1). This disease can be induced by environmental factors (such as bacterial infections and tobacco smoke) and multiple genetic factors (2–4). Commonly, asthma starts with wheezing, but in young children with dysfunctional maturating immune system, not all wheezing progresses to asthma. It has been reported that environmental factors as well as genetic predisposition play important roles in asthma development in children (5,6). Several candidate genes have been reported to be functionally implicated during the occurrence and development of asthma, such as pro-inflammatory genes, anti-inflammatory genes, airway remodeling genes, immune modulation genes, etc. (7).

The ADAM (a disintegrin and metalloproteinase) family, a subgroup of the metzincin metalloproteinase superfamily, plays an important role in physiologic processes, such as cell migration, cell fusion, fertilization and immune response (8,9). ADAM33 (ADAM Metallopeptidase Domain 33) is an asthma susceptible gene, and is associated with asthma and bronchial hyper-responsiveness (10). It is located on the human chromosome 20p13 and is highly polymorphic, containing over 70 single-nucleotide polymorphisms (SNPs) (11). ADAM33 is typically expressed in bronchial smooth muscle cells and human lung fibroblasts. Alterations in ADAM33 activity may influence the function of these cells, thereby resulting in airway remodeling (12). Moreover, airway obstruction and bronchial hyper-reactivity induced by the occurrence of airway remodeling are closely related to asthma (13). Recently, several ADAM33 polymorphisms have been shown to be associated with childhood asthma. For example, Shalaby et al. (14) reported that the rs511898 homozygous mutant genotype and the rs44707 heterozygous genotype of ADAM33 were significantly associated with the risk of childhood asthma. A recent cohort study reported a positive relationship of rs2243250 and rs2070874 polymorphisms with childhood asthma (7). There was no consistent opinion to

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explain the effect of ADAM33 polymorphisms on asthma in children.

In this study, we performed a meta-analysis to examine the association between ADAM33 polymorphism and risk of asthma in children. This study may provide new perspectives in explaining the significance of ADAM33 for predicting the risk of childhood asthma.

**Material and Methods**

**Data source**

Related studies were searched in PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and Embase (http://www.embase.com). Key words used for retrieving were “childhood asthma” or “pediatric asthma” or “asthma in children” and “ADAM33”. The language was restricted to English. The deadline of retrieval was May 2016.

**Inclusion and exclusion criteria**

The included studies met the following inclusion criteria: 1) reported the relationship between ADAM33 polymorphism and risk of asthma in children; and 2) SNP distributions were available in cases and controls for evaluating odds ratio with its 95% confidence interval (CI). Studies were excluded if they were reviews, reports, comments, letters, etc.

**Data extraction**

Two investigators independently extracted the useful information using a standardized form. The following items were extracted: the name of the first author, publication year, geographical location, study year, study type, as well as the gender and age information of the participants, allele frequencies, and number of patients and controls in each SNP (rs511898, rs2280092, rs3918396, rs528557, rs2853209, rs44707, rs2280091 and rs2280089). Divergences were settled by discussion with another investigator.

**Statistical analysis**

We first examined if genotype distribution in control participants was in accordance with the Hardy-Weinberg equilibrium (HWE) in each study by Pearson’s $X^2$ test (15). A meta-analysis was performed with the R statistical package, version 3.12 (https://www.r-project.org/). The association strength between children asthma risk and ADAM33 polymorphisms was estimated by odds ratios (OR) and 95% CI (16). Heterogeneity among studies was detected based on the chi-square Q test and I² test. Heterogeneity was significant when the P value was < 0.1 or I² > 50%, and the random effect model was used to calculate the pooled effect. Otherwise, the fixed effect model was used (17). Publication bias was evaluated by Egger’s method (18).

**Results**

**Study selection**

The flow chart of the selection progress is listed in Figure 1. Briefly, 290 articles were preliminarily identified from PubMed (n=46) and Embase (n=244). Of these, 22 duplicate articles were removed. After reading the titles, abstracts and whole text, if possible, another 224 articles were excluded due to obviously irrelevant data. The studies including both adult asthma and children asthma were also excluded. The abstracts of the remaining articles were carefully read, and 19 of them including 3 letters and 16 case series or case report.

![Figure 1. Flow chart of literature search and study selection.](image-url)
16 case series or case reports were excluded. By reading the full text of the remaining 25 articles, 17 were excluded due to duplicated populations or unavailable data. Finally, a total of 8 eligible studies were included in this meta-analysis (7,14,19–24).

The included studies were published between 2008 and 2016 and were from Saudi Arabia, India, Portugal, Brazil, Czech, Netherlands, Egypt and China (Table 1). There was no significant difference in age and gender among these studies. All were observational studies, including 1 cohort study, 2 cross-sectional pilot studies and 5 case-control studies. The article by Klaassen et al. (7) was based on two types of studies, ADEM (Asthma Detection and Monitoring) study and KOALA study (the Child, Parent and Health: Lifestyle and, Genetic Constitution study). Therefore, the information of these two types of studies were extracted and listed independently in the Tables.

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The SNPs of ADAM33 including rs511898, rs2280092, rs3918396, rs528557, rs2853209, rs44707, rs2280091 and rs2280089 were analyzed in this meta-analysis. Distributions of these genotypes in control and in asthmatic children are listed in Table 2. Genotype distributions of almost all of the control populations were consistent with the HWE.

Meta-analysis

The results regarding the associations between polymorphisms of ADAM33 and asthma risk of children are listed in Table 3 and Supplementary Figures S1–S5. Four genetic models were analyzed for each ADAM33 polymorphism: allele model (wild vs mutation), codominant model (heterozygote vs wild homozygote, mutational homozygote vs wild homozygote), recessive model (wild homozygote vs heterozygote + wild homozygote), and dominant model (wild homozygote+heterozygote vs wild homozygote).

Heterogeneity test was performed for the selection of a suitable model for pooled effect. The meta-analysis results indicated that all the four models of rs2280091 increased the risk of childhood asthma. In the allele model, the rs2280090, rs2280091 and rs44707 polymorphisms increased the risk of childhood asthma, with OR of 1.42 (1.09–1.85), 2.06 (1.45–2.92) and 1.48 (1.25–1.75) respectively. In the codominant model of heterozygote vs wild homozygote, the associations between rs2280091 and rs528557 polymorphisms and asthma in children were significant (OR=1.91, 95%CI=1.24–2.94, and OR=2.92, 95%CI=1.33–6.39, respectively). In the codominant model of mutational homozygote vs wild homozygote, significant results were found in 3 polymorphisms: rs2280091 (OR=4.48, 95%CI=2.93–6.84), rs2787094 (OR=2.12, 95%CI=1.01–4.48), and rs44707 (OR=2.16, 95%CI=1.52–3.07). In the recessive model, the rs2280090 (OR=1.50, 95%CI=1.11–2.02), rs2280091 (OR=2.65, 95%CI=2.08–3.38) and rs44707 (OR=1.68,
Table 2. Distribution of ADAM33 polymorphisms.

| Conventional marking (reference) | SNP        | Wild type | Asthma | Control | X²*   | P       |
|----------------------------------|------------|-----------|--------|---------|-------|---------|
|                                   |            | n WH     | HT      | MH      |       |         |
| Al-Khayyat AI (19)               | rs2280091  | T 96     | 38 47 11| 86 53 28 5| 0.245| 0.6204  |
| T2(G>A)                          | rs2280090  | G 94     | 41 46 7| 84 52 25 7| 2.144| 0.1431  |
| ST+4(A>C)                        | rs44707    | A 99     | 48 46 5 | 60 32 28 0| 5.558| 0.0184  |
| S1(C>T)                          | rs3918396  | C 96     | 90 6 0  | 82 80 2 0| 0.012| 0.9110  |
| Awasthi S (20)                   | rs511898   | G 211    | 34 90 87| 137 33 58 46| 2.910| 0.1058  |
| V4 (G>A)                         | rs2787094  | T 109    | 49 42 16| 45 19 19 7| 0.660| 0.9703  |
| S1 (G>A)                         | rs3918396  | G 98     | 91 7 0  | 105 95 10 0| 0.263| 0.6084  |
| de Faria IJC (22)                | rs528557   | C 88     | 11 38 39| 202 11 136 55| 37.466| <0.001 |
| Godava M (23)                    | rs511898   | G 109    | 32 58 19| 45 15 22 8 | <0.001| 0.3232  |
|                                   | rs2280092  | G 109    | 69 37 3 | 45 31 12 2| 0.324| 0.5694  |
|                                   | rs3918396  | G 109    | 94 15 0 | 45 36 8 1 | 0.384| 0.5353  |
|                                   | rs528557   | C 109    | 49 46 14| 45 21 18 6| 0.444| 0.5052  |
|                                   | rs2853209  | A 109    | 40 49 20| 45 14 22 9| 0.004| 0.4965  |
|                                   | rs44707    | T 109    | 42 51 16| 45 19 19 7| 0.600| 0.9703  |
|                                   | rs2280091  | T 96     | 38 47 11| 86 53 28 5| 0.245| 0.6204  |
|                                   | rs2280090  | G 94     | 41 46 7| 84 52 25 7| 2.144| 0.1431  |
|                                   | rs44707    | A 99     | 48 46 5 | 60 32 28 0| 5.558| 0.0184  |
|                                   | rs3918396  | C 96     | 90 6 0  | 82 80 2 0| 0.012| 0.9110  |
| Klaassen EM1 (7)                 | rs511898   | G 75     | 32 38 5 | 121 40 60 21| 0.334| 0.8533  |
| S2 (C>G)                         | rs285357   | C 76     | 41 35 0 | 122 49 73 0| 3.588| 0.0588  |
| Klaassen EM2 (7)                 | rs511898   | G 56     | 26 21 9 | 169 76 91 2| 23.476| <0.001 |
|                                   | rs285357   | C 55     | 35 20 0 | 176 94 82 0| 1.778| 0.182   |
| Qu SQ (24)                       | rs511898   | G 412    | 178 198 36| 397 173 182 42| 0.333| 0.5637  |
| T1 (C>T)                         | rs2280089  | C 412    | 301 97 14| 397 355 39 3| 1.880| 0.1594  |
| T2(G>A)                          | rs2280090  | G 412    | 319 86 7 | 397 326 69 2| 0.756| 0.3844  |
| T1(T>C)                          | rs2280091  | T 412    | 140 185 87| 397 240 129 28| 3.147| 0.0761  |
| V4(C>G)                          | rs2787094  | C 412    | 141 198 73| 397 232 134 31| 3.259| 0.0710  |
| Q-1(G>A)                         | rs612709   | C 412    | 305 100 7 | 397 307 87 3| 1.620| 0.2031  |
| Shalaby SM (14)                  | rs511898   | G 400    | 77 178 145| 200 58 107 35| 1.427| 0.2323  |
| F+1 (G>A)                        | rs44707    | A 400    | 109 195 96| 200 87 84 29| 1.362| 0.2431  |

SNP: single nucleotide polymorphism; WH: wild homozygote; HT: heterozygote; MH: mutational homozygote; NOS: Newcastle-Ottawa Scale; n: total number of including subjects. *likelihood-ratio X².

95% CI = 1.31–2.16 also showed an association with high risk of childhood asthma. In the dominant model, four polymorphisms increased the risk of asthma in children: rs2280091 (OR = 3.08, 95% CI = 2.06–4.61), rs2787094 (OR = 1.81, 95% CI = 1.34–2.46), rs44707 (OR = 1.59, 95% CI = 1.17–2.15) and rs528557 (OR = 3.30, 95% CI = 1.09–10.02).
Discussion

The present meta-analysis evaluated the relationship between ADAM33 polymorphisms and asthma risk in children. Results showed that in all four genetic models of ADAM33, the rs2280091 polymorphism was associated with the increased risk of childhood asthma. Positive associations were also found between the polymorphisms

### Table 3. Meta-analysis results of association between ADAM33 and childhood asthma.

| SNP          | K            | Test of association OR (95%CI) | Model   | Test of heterogeneity α,β        |
|--------------|--------------|-------------------------------|---------|---------------------------------|
|              | Cases Control |                                |         | Q                  P    | I² (%) |
| Allele model |              |                               |         |                    |       |
| rs2280089    | 1044 884     | 1.68 [0.52–5.42]              | Random  | 11.44 0.0007 91.30 |
| rs2280090    | 1012 962     | 1.42 [1.09–1.85]              | Fixed   | 0.19 0.6594 0      |
| rs2280091    | 1234 1056    | 2.06 [1.45–2.92]              | Random  | 4.35 0.1134 54.10 |
| rs2787094    | 1660 1368    | 1.40 [0.93–2.10]              | Random  | 13.71 0.0033 78.10 |
| rs3918396    | 606 464      | 0.82 [0.46–1.47]              | Fixed   | 2.6 0.2722 23.20 |
| rs44707      | 1638 884     | 1.48 [1.25–1.75]              | Fixed   | 3.25 0.355 7.60   |
| rs511898     | 2526 2138    | 1.22 [0.88–1.68]              | Random  | 29.64 <0.0001 83.10 |
| rs528557     | 816 728      | 2.13 [0.70–6.48]              | Random  | 46.01 <0.0001 95.70 |
| Codominant model 1 | | | | | |
| rs2280089    | 153 60       | 1.36 [0.48–3.88]              | Fixed   | 0.92 0.3379 0      |
| rs2280090    | 146 103      | 1.03 [0.43–2.51]              | Fixed   | 2.68 0.1014 62.7   |
| rs2280091    | 516 312      | 1.35 [0.97–1.88]              | Fixed   | 2.11 0.5499 0      |
| rs2787094    | 582 267      | 1.31 [0.95–1.81]              | Fixed   | 2.08 0.5554 0      |
| rs511898     | 879 667      | 1.59 [0.77–3.30]              | Random  | 32.52 <0.0001 84.6 |
| rs528557     | 330 260      | 2.92 [1.33–6.39]              | Random  | 6.61 0.0366 69.8   |
| Codominant model 2 | | | | | |
| rs2280089    | 386 387      | 2.01 [0.23–17.8]              | Random  | 3.86 0.0495 74.1   |
| rs2280090    | 374 387      | 1.89 [0.78–4.57]              | Fixed   | 1.11 0.2924 9.8    |
| rs2280091    | 347 359      | 4.48 [2.93–6.84]              | Fixed   | 3.34 0.1885 40.1   |
| rs2787094    | 478 453      | 2.12 [1.07–4.48]              | Fixed   | 7.29 0.0631 58.9   |
| rs44707      | 433 252      | 2.16 [1.52–3.07]              | Fixed   | 3.44 0.3287 12.8   |
| rs511898     | 676 534      | 1.71 [0.76–3.85]              | Random  | 34.98 <0.0001 85.7 |
| rs528557     | 239 159      | 3.32 [0.30–36.16]             | Random  | 40.06 <0.0001 95   |
| Recessive model |              |                               |         |                    |       |
| rs2280089    | 522 442      | 1.77 [0.54–5.78]              | Random  | 8.66 0.0033 88.4   |
| rs2280090    | 506 481      | 1.50 [1.11–2.02]              | Fixed   | 1.63 0.2021 38.5   |
| rs2280091    | 617 528      | 2.65 [2.06–3.38]              | Fixed   | 3.28 0.1944 38.9   |
| rs2787094    | 830 684      | 1.56 [0.93–2.64]              | Random  | 12.28 0.0065 75.6  |
| rs3918396    | 303 232      | 0.86 [0.47–1.59]              | Fixed   | 2.37 0.3059 15.6   |
| rs44707      | 819 442      | 1.68 [1.31–2.16]              | Fixed   | 3.24 0.3556 7.5    |
| rs511898     | 1263 1069    | 1.18 [0.88–1.59]              | Random  | 11.51 0.0422 56.5  |
| rs528557     | 539 662      | 1.18 [0.34–4.14]              | Random  | 73.05 <0.0001 94.5 |
| Dominant model |              |                               |         |                    |       |
| rs2280089    | 532 442      | 1.86 [0.25–13.73]             | Random  | 3.29 0.0695 69.6   |
| rs2280090    | 506 481      | 1.46 [0.62–3.44]              | Fixed   | 1.92 0.1658 47.9   |
| rs2280091    | 617 528      | 3.09 [2.06–4.61]              | Fixed   | 2.44 0.2947 18.2   |
| rs2787094    | 830 684      | 1.81 [1.34–2.46]              | Fixed   | 5.68 0.1284 47.2   |
| rs44707      | 819 442      | 1.59 [1.17–2.15]              | Fixed   | 2.92 0.4043 0      |
| rs511898     | 1263 1069    | 1.62 [0.78–3.37]              | Random  | 36.34 <0.0001 86.2 |
| rs528557     | 408 364      | 3.30 [1.09–10.02]             | Random  | 14.97 0.0006 86.6  |

OR: odds ratio; CI: confidence interval; Codominant model 1: heterozygote vs wild homozygote; Codominant model 2: mutational homozygote vs wild homozygote. Random-effects model was used when the P value for heterogeneity test was <0.01, otherwise the fixed-effect model was used. P <0.10 was considered to be statistically significant for Q statistics.
rs2280090 (allele model and recessive model), rs2787094 (codominant model 2 and dominant model), rs44707 (allele model, codominant model 2, recessive model and dominant model) and rs528557 (codominant model 1 and dominant model) and childhood asthma. These data suggest that these ADAM33 polymorphisms may be causative factors for asthma in children.

ADAM33 was first regarded as a susceptibility gene for bronchial hyper-responsiveness and asthma by a genome-wide linkage analysis (25). More than 70 SNPs have been identified in this gene. Some of the asthma-related SNPs are located in regions encoding amino acid changes (26). Others are non-coding SNPs but affect the viability of smooth muscle cells and fibroblasts, affect the inflammation of the airways, and affect the association with other SNPs (26). Therefore, ADAM33 genetic variations may lead to abnormal changes of smooth muscle cells and fibroblasts, thus result in hyper-responsiveness and remodeling of the airway, which is correlated with development of inflammation (13). In a previous meta-analysis, Zheng et al. (27) reported that the ADAM33 rs2280091 polymorphism increased the risk of asthma. The replication of the positive association confirmed the effect of rs2280091 on asthma. However, the meta-analysis by Zheng et al. (27) only illustrated the relationship of one SNP in adults. In the present study, other polymorphisms such as rs2280090, rs2787094, rs44707 and rs528557 were also found to be related to the increased risk of childhood asthma. Although the function of these SNPs in the development of asthma is not fully understood, it is likely that the ADAM33 is an important chemokine in gene mutations that affects the pathogenesis of asthma in children.

Just as other meta-analyses, heterogeneity was found among the articles. The included studies were from different geographical regions, including Asia (Saudi Arabia, India and China), Europe (Portugal, Czech and Netherlands), Africa (Egypt) and America (Brazil), which might contribute to the heterogeneity of genetic diversity. Besides, children in different countries received different medical care, which also influences the phenotype of asthma, and thus might lead to heterogeneity.

Several limitations in this meta-analysis should be pointed out when explaining our results. First, there might be some confounding factors that affect the results of this meta-analysis, we did not perform subgroup analysis because of insufficient data. Second, only studies selected from databases were included, and thus publication bias might exist. We did not perform the publication bias analysis because eligible studies were less than 10. Third, the control group of some included studies were not ideal since a slight deviation from HWE was found. Therefore, more keywords should be used to retrieve more studies for further evaluate the relationship between ADAM33 polymorphism and childhood asthma.

In conclusion, ADAM33 polymorphisms rs2280091, rs2280090, rs2787094, rs44707 and rs528557 were significantly associated with a high risk of childhood asthma.

Supplementary material

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