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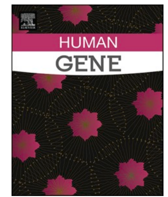

The G allele of the *ADAM33* T1 polymorphism (rs2280091) is a risk factor associated with asthma severity among the Iraqi Arab population

Karrar S. Zayed [a], Bassam K. Kudhair [a,*], Dhifaf Z. Aziz [a], Inam J. Lafta [b]

[a] *Department of Laboratory Investigations, Faculty of Science, University of Kufa, Najaf, Iraq*
[b] *Department of Microbiology, College of Veterinary Medicine, University of Baghdad, Baghdad, Iraq*

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ABSTRACT

Background: The gene encoding a disintegrin and metalloproteinase domain 33 (*ADAM33*) is known to be associated with asthma in different ethnic groups. In Iraq, among the Arab ethnic background, this association has not yet been highlighted.
Methods: One hundred and ninety-two asthmatics were examined; 118 males and 74 females (mean age 38.23 ± 9.13 years). The control group was 183; 110 males and the rest were females. The SNP of rs2280091 A/G (T1) was studied here to determine *adam33* genotyping status using polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP). The level of total IgE was measured using enzyme-linked immunosorbent assay (ELISA).
Results: Significant differences ($p = 0.004$) in the frequencies of the ADAM33 mutant allele carriers between patients and controls were found OR = 1.62 (95% CI 1.16–2.27). This association was significant in individuals who carried homozygous (GG) or heterozygous (AG) variant type genotypes in a reference with carriers of wild-type (AA) genotypes. The odds ratios were 1.70 (95% CI 1.11–2.60, $p = 0.013$), 2.97 (95% CI 1.00–8.75, $p = 0.047$), 1.79 (95% CI 1.18–2.71 $p = 0.005$) for those who carried (wt/vt), (vt/vt), and (wt/vt + vt/vt), respectively. Correlation based on gender shows the presence of a significant association ($p = 0.01$a) for female mutant allele carriers OR = 1.96 (95% CI 1.15–3.36), but not in the case of male. Significant difference ($p = 0.02$) in the frequencies of mutant G allele carrier compared to wild A allele carrier was also found correlated in patients with severe asthma than moderate or mild asthma, OR = 1.78 (95% CI 1.10–2.89). Serum total IgE level in patients with GG genotype (219.37 ± 108.49) was significantly higher than in patients with AG and AA genotypes, respectively (193.22 ± 85.83), (157.11 ± 92.10), ($P = 0.001$).
Conclusions: Carries of GG and AG alleles T1 *ADAM33* polymorphism are at a high risk of developing functional susceptibility of asthma.

1. Introduction

Asthma is a respiratory disease characterized by symptoms and intermittent airway obstruction due to persistent inflammation and remodeling of the airways (Berenguer et al., 2014). Bronchial hyper-responsiveness is a hallmark of the disease. Biosynthetically active myofibroblasts are associated with recurring symptoms, which can be reversible with medication during an attack (Vercelli, 2008;Jie et al., 2011). Asthma affects around 300 million individuals worldwide and is considered a global public health problem, responsible for about 180,000 deaths each year. (Backman et al., 2017).

Several studies suggest that asthma is a genetic disorder resulting from a combination of genetic predisposition and environmental factors. (Bijanzadeh et al., 2011; Grotenboer et al., 2013). Genetic involvement ranges from 48 to 79%, and parental asthma is a significant prognostic factor in childhood asthma (Pinto et al., 2008; Ortiz and Barnes, 2015). Over 100 candidate genes have been linked to asthma, including the adam33 gene, which belongs to the ADAM family of proteins and is involved in various biological activities such as adhesion, proteolysis, signaling, and cell activation (Meyers, 2010; Huovila et al., 2005). The adam33 gene is a member of the ADAM family of proteins, encoding for zinc metalloproteinases, located on chromosome 20p13 (Liang et al., 2013). It consists of 21 introns and 22 exons and produces a protein with eight domains: catalytic, EGF, pre-, transmembrane, disintegrin,

* Corresponding author.
E-mail address: Bassamk.sharuza@uokufa.edu.iq (B.K. Kudhair).

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cytoplasmic, signal, and cysteine-rich domains. These domains are involved in various biological activities that regulate cell adhesion, proteolysis, signaling, activation, and fusion (Van Eerdewegh et al., 2002). These different domains are responsible for many biological activities that modulate adhesion, proteolysis, signaling, cell activation, and fusion (Tripathi et al., 2014). Adam33 is highly expressed in the smooth muscle tissue and fibroblasts of the lungs and its overexpression is associated with airway hyperresponsiveness (Lambrecht and Hammad, 2012).

>100 single nucleotide polymorphisms (SNPs) in the adam33 gene were found, with rs2280091 (T1) located in the cytoplasmic domain. (Serrano et al., 2005; Hirota et al., 2006; Jie et al., 2011; Shen et al., 2017). Studies have investigated the association of rs2280091 as a risk factor for asthma in Caucasians and other ethnic groups, but there is inconclusive data in Asian populations (Van Eerdewegh et al., 2002; Schedel et al., 2006; Blakey et al., 2009; Awasthi et al., 2011; Zhu and Naren, 2017; Zeinaly et al., 2017). Some studies have shown an association between the adam33 T1-associated polymorphism and asthma, while others have not found such an association (Su et al., 2008; Liu et al., 2014; Sun et al., 2017; Farjadian et al., 2018; Ghaemi et al., 2019; Monsalve Mera et al., 2021).

It has been found that serum total immunoglobulin E (IgE) levels are higher in individuals with allergic disorders, including allergic asthma, and can be used to distinguish asthmatic and non-asthmatic individuals (Borish et al., 2005; Sharma et al., 2006; Kovač et al., 2007). Some research indicates a correlation between the adam33 T1 polymorphism and elevated IgE levels in asthmatic patients, but conflicting data exist (Lind et al., 2003; Simpson et al., 2005; Miyake et al., 2012; Godava et al., 2012). Here, we conducted a study to investigate the association between the adam33 T1 polymorphism and asthma as well as IgE levels among Iraqi Arab asthmatics for the first time.

2. Patients and methods

2.1. Study subjects

One hundred and ninety-two asthmatic patients (118 males and 74 females) with mean age (38.23± 9.13) years were recruited from the consulting clinic for tuberculosis and chest diseases in Najaf Governorate during the period from February 2021 to October 2022.

The diagnosis was confirmed by physicians depended on clinical symptoms and laboratory analyses that shown increased serum IgE levels. According to asthma severity, patients were further classified into three groups: mild (66), moderate (73), and severe (53). Patients with any underlying disease except asthma were excluded from the study. All of the enrollees were unrelated and had not taken any long-term control medications prior to enrollment. The controls were 183 (110 males and 73 females) with a mean age (36.23± 8.44) years, who had no apparent health problems and were randomly selected during the sampling period. There were no symptoms or history of asthma or other respiratory disorders in the controls, and IgE levels were all within the normal range.

3. Methods

3.1. Samples collection

Whole blood samples (5 ml) were collected from each participant. EDTA-coated collection vials were used to collect blood samples and stored at ¯20 °C until needed. For DNA extraction, 3 ml was frozen; the rest was left at room temperature for 30–60 min to separate serum, which then used to determine total IgE levels by ELISA assay.

3.2. T1 ADAM33 genotyping

Genomic DNA extraction was performed using DNA Extraction Mini Kit (Qiagen, Hilden, Germany). The T1 polymorphism locus of the *ADAM33* gene (rs2280091) was identified based on the available data of NCBI databases, primers of 5′GTGAATATGGTCAGCAGGAGCC-3′ and 5′CCTGGACTCTTATCACGTTGC-3′ were assigned for RFLP-PCR. The PCR reaction was carried out based on information of the kit supplier (GenetBio, Korea). The reaction volume was 25 μl with a final concentration of 60 ng of genomic DNA template and a final concentration of 0.05 μM for each primer. The PCR protocol was set as follows: 95 °C for 5 min, followed by 35 cycles of 95 °C for 30 s, 56 °C for 30 s, 72 °C for 30 s; the final extension was 72 °C for 10 min. The RFLP reaction was performed with a final volume of 30 μl and contained 1 unit of *NcoI* restriction enzyme (Thermo Fisher Scientific, USA) added to 10 μl of amplified product. The reaction was incubated for 2 h at 37 °C. Results were evaluated on 1.5% agarose gel electrophoresis.

The PCR product (264 bp) contains only one *NcoI* cleavage site. Thus, among those with the normal genotype (AA), treatment of the amplified region with *NcoI* results in product cleavage into two DNA fragments 77 and 187 bp; however, carriers of the homozygous (GG) mutated genotype lose the *NcoI* cleavage site, and thus no digestion occurs. Accordingly, for heterozygous mutant genotype (AG) carriers, the *NcoI*-treated product produces three bands on agarose with weights 264, 187, and 77 bp (Fig. 1).

3.3. IgE measurements

Serum total IgE level was measured using an enzyme-linked immunosorbent assay (ELISA) kit (Sunlongbiotech Cat No.SL0913Hu, China). The microplate reader was set to the optical density (OD) of 450 nm. The OD values of the standards were measured to generate the linear regression equation. The final result was calculated by averaging all of the data measured three times.

3.4. Statistical analysis

Analysis data of genetic and biochemical factors was performed using a statistical package of the social science (SPSS) version 20 software, each variable's values are expressed as mean ± SD. Tukey's multiple comparison test after a One-Way Analysis of Variance (ANOVA) is performed to evaluate the data. Odds ratios (OR) with 95% confidence intervals (CI) were used to evaluate the relative risk associated with rare alleles, Minor allele frequency (MAF) was calculated by SNPStates software. The “P” value was considered significant at <0.05.

4. Results

There were no significant differences based on gender and age (P = 0.51 and 0.37, respectively). However, asthmatic patients showed a significant higher IgE level compared to the control group (241.79 ± 122.81 *vs.* 139.46 ± 63.55) (p = 0.0001) (Table 1).

The frequency of GG and AG genotypes in asthmatic patients was statistically significantly higher than in the control group, OR = 2.97 (95CI 1.00–8.75, p = 0.047), OR = 1.70 (95CI 1.11–2.60, p = 0.013) respectively. In addition, the distribution frequency of G allele carriers was significantly higher in patient than control comparing with the reference, the A allele carriers OR = 1.62 (95CI 1.16–2.27, p = 0.0047) (Table 2). Results also shows that there was no significant association between any of GG, AG, and AA genotypes and patients' gender; However, statistically the genotypes distribution of (wt/vt + vt/vt) is significantly (p = 0.026) correlated with female asthmatic patients in compare with wild type genotype of AA, OR = 2.11(95CI 1.09–4.07). Therefore, the G allele carriers showed significantly higher distribution in female patients than control, OR = 1.96 (95CI 1.15–3.36, p = 0.014) (Table 3). Similarly, the association of genotyping with asthma severity showed no association in regards with any of the three genotypes; However, the G allele carriers showed significantly higher distribution in patients with the severe type of asthma than control, OR = 1.78 (95CI

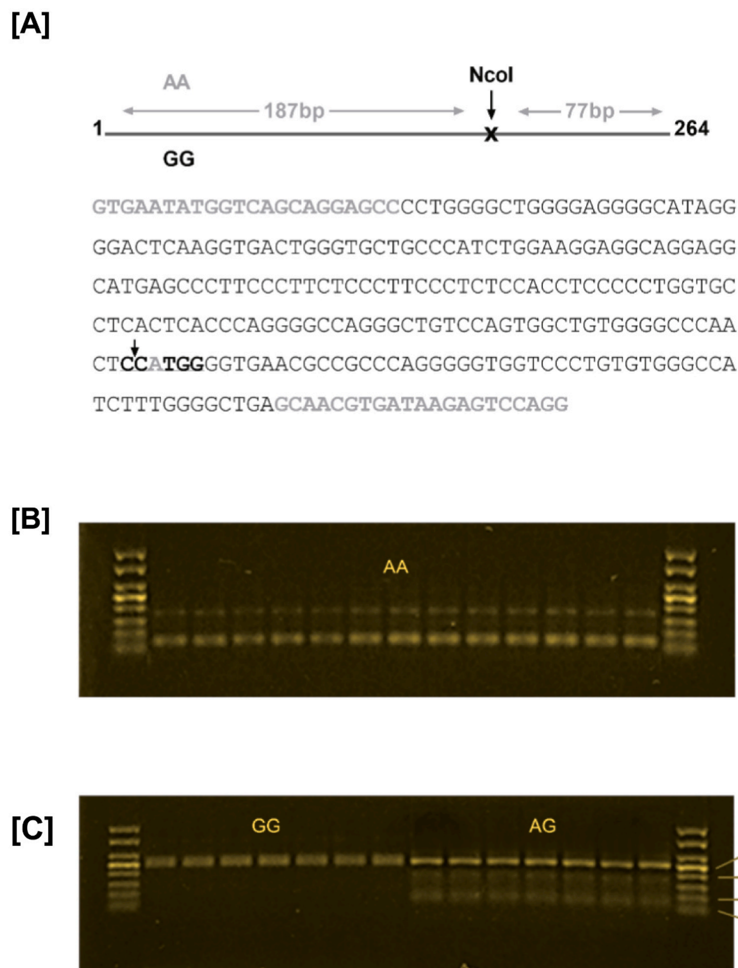

Fig. 1. PCR–RFLP assay to determine the *ADAM33* T1 (rs2280091 A > G Exon 20) SNP. The amplicon of *ADAM33* (264 bp) were digested with *NcoI*, the cleavage site is present in the wild type (A) allele generating two fragments (187 and 77 bp), unlike the variant (G) allele which gives a single species due to the abolition of the *NcoI* recognition sequence. [A] Schematic diagram of *ADAM33* amplicon digested with *Ncoi.* DNA sequencing was obtained using NCBI accession version NC_000020.11, the gray colour of the beginning and the end of amplicon sequence represents the primers binding sites, bold black sequence of CCATGG represented the recognition sequence of *NcoI,* the grayed colour A nucleotide (wild allele) represents the SNP position. [B] and [C] Agarose gel electrophoresis of *NcoI* treated *ADAM33* amplicon of AA in [B], AG, and GG genotypes in [C].

Table 1
Clinical characteristics of asthma patients and control group.

	Case ($n = 192$)	Control ($n = 183$)	p*
	n (%)	n (%)	
Gender			
Male	(61.46) 118	110 (60.10)	0.51
Female	(38.54) 74	73 (39.90)	
Age (mean ± SD)	38.23 ± 9.13	36.23 ± 8.44	0.37
Severity of asthma			
Mild	37 (19.2)	–	
Moderate	51 (26.6)	–	–
Severe	104 (54.2)	–	
IgE (mean ± SD) IU/mL	241.79 ± 122.81	139.46± 63.55	0.0001*

* Chi-squared p value.

Table 2
Frequencies of T1 *ADAM33* genotypes in asthmatic patients and control.

T1 Genotype	Case (n = 192) n (%)	Control (n = 183) n (%)	OR (95% CI)	p*
AA	92 (47.91)	114 (62.29)	Reference	
AG	88 (45.83)	64 (34.97)	1.70 (1.11–2.60)	0.0136*
GG	12 (6.26)	5 (2.74)	2.97(1.00–8.75)	0.0477*
AG + GG	100 (52.09)	69 (37.71)	1.79 (1.18–2.71)	**0.0053***
A carrier	272 (70.83)	292 (97.78)	Reference	
G carrier	112 (29.17)	74 (20.21)	1.62 (1.16–2.27)	**0.0047***

* Chi-squared p value.

1.10–2.89, $p = 0.02$) (Table 4). Finally, carrier patients of GG genotype showed a significantly increased IgE level than carriers of AG and AA genotypes (219.37 ± 108.49) *vs* (193.22 ± 85.83 and 157.11 ± 92.10), ($p = 0.001$) respectively (Table 5).

5. Discussion

The significance of the *ADAM33* T1 polymorphism in asthma susceptibility has not been revealed before in the Iraqi Arab population. The G/G, A/G, and G alleles of *ADAM33* have been linked to an increased risk of asthma. Our results are consistent with those found in previous studies involving a variety of ethnic groups for example in Asians such as China (Jie et al., 2011; Qu et al., 2011; Liu et al., 2014; Wang et al., 2014; Deng et al., 2017; Sun et al., 2017), Mongolia (Zhu et al., 2018), Sudia (Al-Khayyat et al., 2012), other ethnic groups; like the Caucasian populations of White Americans (Howard et al., 2003), Germans (Werner et al., 2004), British (Simpson et al., 2005), Colombians (Vergara et al., 2010), and Peruvians (Monsalve Mera et al., 2021).

The role of T1 *ADAM33* polymorphism in the development of asthma has not been thoroughly revealed. The *ADAM33* T1 polymorphism was found to be significantly associated with decreased lung function in children and increased cytokines, loss of lung function, and inflammatory cells in individuals with chronic obstructive pulmonary disease (COPD), which is another inflammatory disease with the same etiology of asthma (Simpson et al., 2005). Substitution of methionine with threonine (Met764Thr) due to the A > G ADAM33 T1 polymorphism in

Table 3
Association between gender of asthma patients and T1 *ADAM33* genotypes.

	Male			Female		
Genotype	Ca(n:118) / Co(n:110) n (%)/n (%)	OR (95% CI)	p*	Ca(n:74) / Co(n:73) n (%)/n (%)	OR (95% CI)	p*
AA	60(50.8) / 69(62.7)	Reference		32(43.2) / 45(61.7)	Reference	
AG	51(43.3) / 36(32.7)	1.63 (0.94–2.82)	0.081	37(50.0) / 28(38.4)	1.86 (0.95–3.62)	0.069
GG	7(5.9) / 5(4.6)	1.61 (0.49–5.33)	0.43	5(6.8) / 0	–	–
AG + GG	58(49.2) / 41(37.3)	1.63 (0.96–2.76)	0.07	42(56.8) / 28(38.4)	2.11 (1.09–4.07)	**0.026***
A carrier	171(72.5) / 174(79.1)	Reference		101(68.2)/118(80.8)	Reference	
G carrier	65(27.5) / 46(20.9)	1.44 (0.93–2.22)	0.10	47(31.8) /28(19.2)	1.96 (1.15–3.36)	**0.014***

* Chi-squared p value.

Table 4
The association between T1 ADAM33 genotypes and asthma severity.

	Control (n = 183)	Mild (n = 66)			Moderate (n = 73)			Severe (n = 53)		
	n (%)	n (%)	OR (95% CI)	p*	n (%)	OR (95% CI)	p*	n (%)	OR (95% CI)	p*
AA	114 (62.29)	32 (48.49)	OR (95% CI)		36 (49.32)	Reference		24 (45.28)	Reference	
AG	64 (34.97)	31 (46.97)	Reference	0.07	32 (43.83)	1.58 (0.90–2.79)	0.11	25 (47.17)	1.86(0.98–3.51)	0.06
GG	5 (2.74)	3 (4.54)	1.73 (0.97–3.09)	0.32	5 (6.85)	3.16 (0.87–11.56)	0.08	4 (7.55)	3.80 (0.95–15.20)	0.06
AG + GG	69 (37.71)	34 (51.51)	2.14 (0.48–9.43)	0.05	37 (50.68)	1.69 (0.98–2.94)	0.06	29 (54.72)	2.00 (1.07–3.70)	**0.03***
A carrier	292 (79.78)	105 (73.94)	1.76 (0.99–3.10)		104 (71.23)	Reference		73 (68.87)	Reference	
G carrier	74 (20.22)	37 (26.06)	Reference	0.15	42 (28.77)	1.59 (1.03–2.47)	0.04	33 (31.13)	1.78 (1.10–2.89)	**0.02***

* Chi-squared p value.

Table 5
IgE level in asthmatics according to T1 ADAM33 genotypes.

Clinical characteristic	Genotype			p
	GG(n = 12)	AG(n = 88)	AA(n = 92)	
IgE level (IU/mL)(mean ± SD)	219.37 ± 108.49	193.22 ± 85.83	157.11 + 92.10	0.001*

* Chi-squared p value.

exon 20 can alter intracellular signaling, which may increase fibroblast proliferation and differentiation, which are hallmarks of asthmatic airway remodeling (Lee and Song, 2012; Tripathi et al., 2014; Al-Khayyat et al., 2012). Furthermore, the soluble form of *ADAM33* is found to stimulate neovascularization *in vivo* and endothelial cell differentiation *in vitro*, indicating that *ADAM33* can promote angiogenesis and airway remodeling. In addition to its role in differentiation, cell growth, and control of the immune system, TGFβ has been considered as a key mediator of airway remodeling as a multifunctional cytokine (Peng et al., 2011).

Human allergic diseases is more likely to be developed when TGFβ1 signaling is disturbed. It was found that asthmatic patients and experimental animals with allergic airway inflammation have increased TGFβ1 activity. Active TGFβ1 likely promotes fibroblast proliferation and differentiation leading to airway remodeling by modulating *ADAM33* expression and by promoting shedding of the ectodomain of *ADAM33* (Frischmeyer-Guerrerio et al., 2013). Different *ADAM33* isoforms are found in human embryonic bronchi and their adjacent mesenchyme, indicating of their role in smooth muscle development. Mesenchymal tissues may also be a source of the “unusual” airway development that leads to childhood asthma. As a consequence, a SNP that modifies the catalytic domain of ADAM33 may influence asthma etiology. Since higher ADAM33 levels produce persistent airflow obstruction, genetic variation in this gene has been associated with an accelerated decrease in pulmonary function. Thus, *ADAM33* has become not only an asthma susceptibility gene as well as a biomarker of asthma severity (Jongepier et al., 2004).

Here, an increased incidence among G allele carriers was found in patients with severe asthma, which is consistent with other studies (Foley et al., 2007; Jie et al., 2009; Li et al., 2019). Ectodomain shedding due to the *ADAM33* T1 polymorphism in severe asthmatics may developed a higher expression of the *ADAM33* (Foley et al., 2007; Tripathi et al., 2014). Which may explain the significantly elevated IgE level in patients, particularly in asthmatics carriers of GG genotype of T1 *ADAM33* in our study, which is also consistent with several studies worldwide (Bijanzadeh et al., 2010; Chiang et al., 2012; El-Falaki et al., 2013; Lama et al., 2013; Miyake et al., 2012; Naqvi et al., 2007; Vergara et al., 2010; Zihlif et al., 2021). However, further investigations are needed, for example studying the association of gene expression of T1 ADAM33 carriers among asthmatic patients with respect to IgE levels. This is required to reveal the reasons behind the controversial findings indicating no associations such as those reported in Puerto and Mexican populations (Lind et al., 2003), Czechs (Bijanzadeh et al., 2010), Iran (Karimi et al., 2014), and china (Yin et al., 2010).

The importance *ADAM33* comes from possible association with immune response, for example it enhances the risk of immunological responses mediated by T-helper 2 cells and inflammation (Vergara et al., 2010). The G polymorphism in *ADAM33* could impair the shedding of growth factor receptors, which could contribute to a shift to an immunological response mediated by type 2 helper T cells or increased inflammation (Shapiro, 2002). It is also reported to play an important role in intercellular adhesion. The disintegrin domain of *ADAM33* supports the expression of integrin in mesenchymal cells, such as smooth muscle cells and fibroblasts which leads to α9β1 integrin-dependent leukocyte adhesion (Werner et al., 2004). *ADAM33* disintegrin domain SNPs may affect airway inflammation and leukocyte numbers, both of which are usually reflected on the IgE, as well as intercellular adhesion, (Wiester and Giachelli, 2003).

6. Conclusion

The importance of *ADAM33* G allele in the T1 polymorphism is reported here for the first time in Iraq among Arab ethnicity. The association revealed here suggest the possibility of applying rs2280091 as a risk factor of asthma. According to our findings, the *ADAM33* G allele in the T1 polymorphism is a strong predictor of asthma among Iraqi Arab ethnicity.

Ethical approval

To fulfill the requirements of the local and/or national research committee, all procedures employed in studies involving human participants were in compliance with the 1964 Helsinki statement and its consequent revisions or a similar ethical standard. In addition, each participant signed a formal consent form.

Authors' contributions

The lead author of the study, KZK, conducted all the experiments, DZA also conducted some experiments. IJL analyzed the data. BKK was responsible for designing and supervising the study. All authors participated in writing the manuscript, with BKK being the one to write the final version.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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References

Al-Khayyat, A.I., Al-Anazi, M., Warsy, A., Vazquez-Tello, A., Alamri, A.M., Halwani, R., Alangari, A., Al-Frayh, A., Hamid, Q., Al-Muhsen, S., 2012. T1 and T2 ADAM33 single nucleotide polymorphisms and the risk of childhood asthma in a Saudi Arabian population: a pilot study. Ann Saudi Med. 32 (5), 479–486.

Awasthi, S., Tripathi, P., Ganesh, S., Husain, N., 2011. Association of ADAM33 gene polymorphisms with asthma in Indian children. J. Hum.Genet. 56 (3), 188–195.

Backman, H., Räisänen, P., Hedman, L., Stridsman, C., Andersson, M., Lindberg, A., Lundbäck, B., Rönmark, E., 2017. Increased prevalence of allergic asthma from 1996 to 2006 and further to 2016—results from three population surveys. Clin.Exp. Allergy. 47 (11), 1426–1435.

Berenguer, A.G., Fernandes, A.T., Oliveira, S., Rodrigues, M., Ornelas, P., Romeira, D., Serrão, D., Rosa, A., Câmara, R., 2014. Genetic polymorphisms and asthma: findings from a case–control study in the Madeira island population. Biol. Res. 47 (1), 1–11.

Bijanzadeh, M., Ramachandra, N.B., Mahesh, P.A., Savitha Mysore, R., Kumar, P., Manjunath, B.S., Jayaraj, B.S., 2010. Association of IL-4 and ADAM33 gene polymorphisms with asthma in an Indian population. Lung 188 (5), 415–422.

Bijanzadeh, M., Mahesh, P.A., Ramachandra, N.B., 2011. An understanding of the genetic basis of asthma. Indian J. Med. Res. 134 (2), 149.

Blakey, J.D., Sayers, I., Ring, S.M., Strachan, D.P., Hall, I.P., 2009. Positionally cloned asthma susceptibility gene polymorphisms and disease risk in the British 1958 birth cohort. Thorax 64 (5), 381–387.

Borish, L., Chipps, B., Deniz, Y., Gujrathi, S., Zheng, B., Dolan, C.M., TENOR Study Group, 2005. Total serum IgE levels in a large cohort of patients with severe or difficult-to-treat asthma. Ann. Allergy Asthma Immunol. 95 (3), 247–253.

Chiang, C.H., Lin, M.W., Chung, M.Y., Yang, U.C., 2012. The association between the IL-4, ADRβ2, and ADAM 33 gene polymorphisms and asthma in the Taiwanese population. J Chin Med Assoc. 75 (12), 635–643.

Deng, R., Zhao, F., Zhong, X., 2017. T1 polymorphism in a disintegrin and metalloproteinase 33 (ADAM33) gene may contribute to the risk of childhood asthma in Asians. Inflamm. Res. 66 (5), 413–424.

El-Falaki, M.M., Wilson, M.M., Ezzat, G.M., Mokhtar, D.A., El Baz, M.S., Hamed, D.H., 2013. A disintegrin and metalloproteinase 33 (ADAM33) gene polymorphism association with asthma in Egyptian children. Egypt J Med Hum Genet 14 (1), 55–62.

Farjadian, S., Moghtaderi, M., Hoseini-Pouya, B.A., Ebrahimpour, A., Nasiri, M., 2018. ADAM33 gene polymorphisms in southwestern Iranian patients with asthma. Iranian J Basic Med Sci. 21 (8), 813.

Foley, S.C., Mogas, A.K., Olivenstein, R., Fiset, P.O., Chakir, J., Bourbeau, J., Ernst, P., Lemière, C., Martin, J., Hamid, Q., 2007. Increased expression of ADAM33 and ADAM8 with disease progression in asthma. J. Allergy Clin. Immunol. 119 (4), 863–871.

Frischmeyer-Guerrerio, P.A., Guerrerio, A.L., Oswald, G., Chichester, K., Myers, L., Halushka, M.K., Oliva-Hemker, M., Wood, R., Dietz, H.C., 2013. TGFβ receptor mutations impose a strong predisposition for human allergic disease. Sci. Transl. Med. 5 (195), 195ra94-195ra94.

Ghaemi, M.R., Hemmati, S., Rezaei, A., Sadr, M., Mohebbi, B., Ghaffaripour, H., Rezaei, N., Mahdaviani, S.A., 2019. Association of ADAM33 T1 polymorphism with subgroups of pediatric asthma patients in Iran. Acta Medica Iranica 635–639.

Godava, M., Kopriva, F., Bohmova, J., Vodicka, R., Dusek, L., Cvanova, M., Muzik, J., Markova, M., Schneiderova, E., Vrtel, R., 2012. Association of STAT6 and ADAM33 single nucleotide polymorphisms with asthma bronchial and IgE level and its possible epigenetic background. Biomed. Pap. Med. Fac. Univ. Palacky Olomouc Czech Repub. 156 (3), 236–247.

Grotenboer, N.S., Ketelaar, M.E., Koppelman, G.H., Nawijn, M.C., 2013. Decoding asthma: translating genetic variation in IL33 and IL1RL1 into disease pathophysiology. J. Allergy Clin. Immunol. 131 (3), 856–865.

Hirota, T., Hasegawa, K., Obara, K., Matsuda, A., Akahoshi, M., Nakashima, K., Shirakawa, T., Doi, S., Fujita, K., Suzuki, Y., Nakamura, M., Tamari, M., 2006. Association between ADAM33 polymorphisms and adult asthma in the Japanese population. Clin. Exp. Allergy 36 (7), 884–891.

Howard, T.D., Postma, D.S., Jongepier, H., Moore, W.C., Koppelman, G.H., Zheng, S.L., Xu, J., Bleecker, E., Meyers, D.A., 2003. Association of a disintegrin and metalloprotease 33 (ADAM33) gene with asthma in ethnically diverse populations. J. Allergy Clin. Immunol. 112 (4), 717–722.

Huovila, A.P.J., Turner, A.J., Pelto-Huikko, M., Kärkkäinen, I., Ortiz, R.M., 2005. Shedding light on ADAM metalloproteinases. Trends Biochem. Sci. 30 (7), 413–422.

Jie, Z., Jin, M., Cai, Y., Bai, C., Shen, Y., Yuan, Z., Hu, Y., Holgate, S., 2009. The effects of Th2 cytokines on the expression of ADAM33 in allergen-induced chronic airway inflammation. Respir. Physiol. Neurobiol. 168 (3), 289–294.

Jie, Z., Hu, Z., Bai, C., Jin, M., 2011. ADAM33 gene polymorphisms associate with asthma susceptibility and severity in East China han population. J. Asthma 48 (10), 979–985.

Jongepier, H., Boezen, H.M., Dijkstra, A., Howard, T.D., Vonk, J.M., Koppelman, G.H., Zheng, S.L., Meyers, D.A., Bleecker, E., R., Postma, D. S., 2004. Polymorphisms of the ADAM33 gene are associated with accelerated lung function decline in asthma. Clin. Exp. Allergy 34 (5), 757–760.

Karimi, M.R.Z., Faridhosseini, R., Abbaszadegan, M.R., 2014. Association of ADAM33 gene polymorphisms with allergic asthma. Iran J Basic Med Sci 17 (9), 716.

Kovač, K., Dodig, S., Tješić-Drinković, D., Raos, M., 2007. Correlation between asthma severity and serum IgE in asthmatic children sensitized to Dermatophagoides pteronyssinus. Arch. Med. Res. 38 (1), 99–105.

Lama, M., Chatterjee, M., Chaudhuri, T.K., 2013. Total serum immunoglobulin e in children with asthma. Indian J. Clin. Biochem. 28 (2), 197–200.

Lambrecht, B.N., Hammad, H., 2012. The airway epithelium in asthma. Nat. Med. 18 (5), 684–692.

Lee, Y.H., Song, G.G., 2012. Association between ADAM33 T1 polymorphism and susceptibility to asthma in Asians. Inflamm. Res. 61 (12), 1355–1362.

Li, H.F., Yan, L.P., Wang, K., Li, X.T., Liu, H.X., Tan, W., 2019. Association between ADAM33 polymorphisms and asthma risk: a systematic review and meta-analysis. Respir. Res. 20 (1), 1–18.

Liang, S., Wei, X., Gong, C., Wei, J., Chen, Z., Deng, J., 2013. A disintegrin and metalloprotease 33 (ADAM33) gene polymorphisms and the risk of asthma: a meta-analysis. Hum. Immunol. 74 (5), 648–657.

Lind, D.L., Choudhry, S., Ung, N., Ziv, E., Avila, P.C., Salari, K., Lovins, E.G., Coyle, N.E., Nazario, S., Burchard, E.G., 2003. ADAM33 is not associated with asthma in Puerto Rican or Mexican populations. Am. J. Respir. Crit. Care Med. 168 (11), 1312–1316.

Liu, Y., Wang, Z.H., Zhen, W., Lu, S.J., Liu, Z., Zou, L.Y., Xu, J.J., 2014. Association between genetic polymorphisms in the ADAM33 gene and asthma risk: a meta-analysis. DNA Cell Biol. 33 (11), 793–801.

Meyers, D.A., 2010. Genetics of asthma and allergy: what have we learned? J. Allergy Clin. Immunol. 126 (3), 439–446.

Miyake, Y., Tanaka, K., Arakawa, M., 2012. ADAM33 genetic polymorphisms, smoking, and rhinoconjunctivitis in Japanese women: the Kyushu Okinawa maternal and child health study. Hum. Immunol. 73 (4), 411–415.

Monsalve Mera, A., Arrascue Vega, C., Menendez Nuñez, R., Celestino-Segura, W., Serquén López, L., 2021. Characterization of the V4 and T1 polymorphism of the ADAM33 gene and its association with the development of asthma. Revista de la Facultad de Medicina Humana 21 (2), 5.

Naqvi, M., Choudhry, S., Tsai, H., Thyne, S., Navarro, D., Nazario, S., Rodriguez-Santana, J., Casal, J., Torres, A., Chapela, R., Watson, H., Meade, K., Rodriguez-Cintron, W., Lenoir, M., Avila, P., Burchard, E., 2007. Association between IgE levels and asthma severity among African American, Mexican, and Puerto Rican patients with asthma. J. Allergy Clin. Immunol. 120 (1), 137–143.

Ortiz, R.A., Barnes, K.C., 2015. Genetics of allergic diseases. Immunol. Allergy Clin. N. Am. 35 (1), 19–44.

Peng, X., Mathai, S.K., Murray, L.A., Russell, T., Reilkoff, R., Chen, Q., Gulati, M., Elias, J., Bucala, R., Gan, Y., Herzog, E.L., 2011. Local apoptosis promotes collagen production by monocyte-derived cells in transforming growth factor β1-induced lung fibrosis. Fibrogenesis Tissue Repair 4 (1), 1–13.

Pinto, L.A., Stein, R.T., Kabesch, M., 2008. Impact of genetics in childhood asthma. J. Pediatr. 84 (4), S68–S75.

Qu, S., Sun, D., Wang, Y., Zhang, C., Lv, Y., Yao, L., 2011. Association of ADAM33 polymorphisms with childhood asthma in a northern Chinese population. Exp. Mol. Pathol. 91 (3), 775–779.

Schedel, M., Depner, M., Schoen, C., Weiland, S.K., Vogelberg, C., Niggemann, B., Lau, S., Illig, T., Klopp, N., Wahn, U., Mutius, E., Nickel, R., Kabesch, M., 2006. The role of polymorphisms in ADAM33, a disintegrin and metalloprotease 33, in childhood asthma and lung function in two German populations. Respir. Res. 7 (1), 1–12.

Serrano, C., Valero, A., Picado, C., 2005. Rhinitis and asthma: one airway, one disease. Arch. Bronconeumol. 41, 569–578.

Shapiro, S., 2002. ADAM33 surfaces as an asthma gene. N. Engl. J. Med. 347, 936–938.

Sharma, S., Kathuria, P.C., Gupta, C.K., Nordling, K., Ghosh, B., Singh, A.B., 2006. Total serum immunoglobulin E levels in a case-control study in asthmatic/allergic

patients, their family members, and healthy subjects from India. Clin. Exp. Allergy 36 (8), 1019–1027.
Shen, B., Lin, R., Wang, C.C., Rei, J., Sun, Y., Yang, Y.L., Lin, Y.Y., 2017. ADAM33 gene polymorphisms identified to be associated with asthma in a Chinese Li population. Biomed. Rep. 6 (3), 323–328.
Simpson, A., Maniatis, N., Jury, F., Cakebread, J.A., Lowe, L.A., Holgate, S.T., Woodcock, A., Ollier, W., Collins, A., Custovic, A., Holloway, J., John, S.L., 2005. Polymorphisms in a disintegrin and metalloprotease 33 (ADAM33) predict impaired early-life lung function. Am. J. Respir. Crit. Care Med. 172 (1), 55–60.
Su, D., Zhang, X., Sui, H., Lü, F., Jin, L., Zhang, J., 2008. Association of ADAM33 gene polymorphisms with adult allergic asthma and rhinitis in a Chinese Han population. BMC Med. Genet. 9 (1), 1–6.
Sun, F.J., Zou, L.Y., Tong, D.M., Lu, X.Y., Li, J., Deng, C.B., 2017. Association between ADAM metallopeptidase domain 33 gene polymorphism and risk of childhood asthma: a meta-analysis. Braz. J. Med. Biol. Res. 50 (10), e6148.
Tripathi, P., Awasthi, S., Gao, P., 2014. ADAM metallopeptidase domain 33 (ADAM33): a promising target for asthma. Mediat. Inflamm. 572025.
Van Eerdewegh, P., Little, R.D., Dupuis, J., Del Mastro, R.G., Falls, K., Simon, J., Keith, T. P., 2002. Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. Nature 418 (6896), 426–430.
Vercelli, D., 2008. Discovering susceptibility genes for asthma and allergy. Nat. Rev. Immunol. 8, 169–182.
Vergara, C.I., Acevedo, N., Jiménez, S., Martínez, B., Mercado, D., Gusmão, L., Barnes, K. C., Caraballo, L., 2010. A six-SNP haplotype of ADAM33 is associated with asthma in a population of Cartagena, Colombia. Int. Arch. Allergy Immunol. 152 (1), 32–40.
Wang, J., Simayi, M., Wushouer, Q., Xia, Y., He, Y., Yan, F., Wen, H., 2014. Association between polymorphisms in ADAM33, CD14, and TLR4 with asthma in the Uygur population in China. Genet. Mol. Res. 13 (2), 4680–4690.
Werner, M., Herbon, N., Gohlke, H., Altmüller, J., Knapp, M., Heinrich, J., Wjst, M., 2004. Asthma is associated with single-nucleotide polymorphisms in ADAM33. Clin. Exp. Allergy 34 (1), 26–31.
Wiester, L.M., Giachelli, C.M., 2003. Expression and function of the integrin alpha9beta1 in bovine aortic valve interstitial cells. J. Heart Valve Dis. 12 (5), 605–616.
Yin, Y., Wang, A.H., Chen, P., Liu, Q.J., 2010. Association between ADAM33 gene polymorphism and chronic obstructive pulmonary disease. Chin. J. Nosocomiol. 20, 1840–1843.
Zeinaly, I., Sadeghi-Shabestrai, M., Babaloo, Z., Razavi, A., Sajay-Asbaghi, M., Sadigh-Eteghad, S., Kazemi, T., 2017. Investigating the association of ADAM33 single nucleotide polymorphisms (SNPs) with susceptibility to allergic asthma in Azerbaijan population of Iran: a case-control study. Iran J Allergy Asthma Immunol. 378–385.
Zhu, S., Naren, G., 2017. Association between polymorphism of T1 locus allele in ADAM33 gene and bronchial asthma in Inner Mongolia Han and Mongolian population. J. Clin. Pulmonary Med. 22, 61–64.
Zhu, S., Li, P., Suo, H., Dong, J., Cui, L., 2018. Association of ADAM33 gene polymorphisms with asthma in Mongolian and Han groups in Inner Mongolia. Saudi J. Bio. Sci. 25 (8), 1795–1799.
Zihlif, M., Imraish, A., Al-Rawashdeh, B., Qteish, A., Husami, R., Husami, R., Tahboub, F., Jarrar, Y., Lee, S.J., 2021. The association of IgE levels with ADAM33 genetic polymorphisms among asthmatic patients. J. Personal. Med. 11 (5), 329.