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CHARACTERIZATION OF THE V4 AND T1 POLYMORPHISMS OF *ADAM33* GENE AND ITS ASSOCIATION WITH THE DEVELOPMENT OF ASTHMA

CARACTERIZACIÓN DEL POLIMORFISMO V4 Y T1
DEL GEN ADAM33 Y SU ASOCIACIÓN CON EL DESARROLLO DEL ASMA

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ABSTRACT

Objectives: To determine the association between the presence of V4 polymorphisms of the *ADAM33* gene and asthma disease and to describe the frequency of T1 polymorphism in patients from a hospital in the Lambayeque region. **Method:** Design of cases and controls. Location: Hospital Almanzor Aguinaga Asenjo - EsSalud, level of complexity III-1. Population: patients between 5-17 years old attended by an outpatient clinic. The cases were patients diagnosed according to the Global Initiative for Asthma (GINA) 2016 guidelines. Controls were patients without a diagnosis of any chronic lung disease or a family history of asthma. **Results:** In most cases, both cases and controls did not present the V4 polymorphism, I feel positive only in 46% of cases and 31% of controls. When the association between the V4 polymorphism and the presence of asthma was evaluated, the OR was 1.93 (95% CI: 0.62 - 6.00), with a non-significant value (p = 0.196) for the Xi test --Pearson square. However, the T1 polymorphism was present in 87% of cases; and the proportion of Tumbesinos with the mutation was much lower than that of other regions. **Conclusions:** No association was found between the V4 polymorphism and the presence of asthma in patients from a Lambayeque hospital. The T1 polymorphism occurs quite frequently in asthmatic patients at Hospital Almanzor Aguinaga Asenjo - ESSalud.

Key words: Asthma; SNPs; ADAM proteins (source: MeSH NLM).

RESUMEN

Objetivos: Determinar asociación entre la presencia de los polimorfismos V4 del gen *ADAM33* y la enfermedad del asma y describir la frecuencia del polimorfismo T1 en pacientes de un hospital de la región Lambayeque. **Métodos:** Diseño de casos y controles. Escenario: Hospital Almanzor Aguinaga Asenjo – EsSalud, nivel de complejidad III-1. Población: pacientes entre 5-17 años atendidos por consultorio externo. Los casos fueron los pacientes diagnosticados según las directrices de Global Initiative for Asthma (GINA) 2016. Los controles fueron pacientes sin diagnóstico de alguna enfermedad pulmonar crónica ni antecedentes familiares de asma. **Resultados:** En su mayoría tanto casos como controles no presentaron el polimorfismo V4, siento positivo solo en el 46% de los casos y 31% de los controles. Cuando se evaluó la asociación entre el polimorfismo V4 y la presencia de asma, el OR fue de 1,93 (IC95%: 0,62 – 6,00), con un valor no significativo (p = 0,196) para la prueba de Xi-cuadrado de Pearson. Sin embargo, el polimorfismo T1 estuvo presente en el 87% de casos; y la proporción de tumbesinos con la mutación fue mucho más baja que la de otras regiones. **Conclusión:** No se encontró asociación entre el polimorfimo V4 y la presencia de asma en pacientes de un hospital de Lambayeque. El polimorfismo T1 se presenta con bastante frecuencia en los pacientes asmáticos del hospital Hospital Almanzor Aguinaga Asenjo – ESSalud.

Palabras clave: Asma; polimorfismo genético y en *ADAM33* (fuente: DeCS BIREME).

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INTRODUCCIÓN

Asthma is the most common chronic disease among children[1,2].Worldwide, in children, it has increased 200% in the last 20 years[3] In Latin America, Peru is in the intermediate prevalences group with 21.47%[4] A study of children in Ica, found a prevalence of 13.5% of this disease, predominating children under 5 years (39%)[5] In Chiclayo province , department of Lambayeque, in 2017, it was reported 622 cases of asthma, with 52% being children under 11 years of age and for 2018 the Almanzor Aguinaga Asenjo Hospital reported 331 cases of allergic asthma[6].

The incidence of asthma increases as communities adopt Western lifestyle and urbanize[7]. Although there are many triggering risk factors such as exposure to aeroallergens 8 and viral infections, what finally generate this disease is the idiosyncrasy of the population with environmental ang genetic factors[3,9-11].

Numerous studies have shown that the V4 polymorphism in the *ADAM33* gene is significantly related to susceptibility to asthma[1,4,12–16], as well as with the accelerated decrease in forced expiratory volume in the first second (FEV1) in spirometry[17,18]; however, these associations change depending on ethnicgroup19Forinstance,inShanghaiandShandog (China) it was shown that in Caucasian and Asian populations the V4 polymorphism was associated with asthma, Furthermore, in the subgroups analysis by source of controls, significant associations were found between this polymorphism and the risk of asthma in population and hospital subgroups[14,20] Likewise, in the Uyghur population (China) it was demonstrated that polymorphisms T2 (AG + AA) and V4 (CG + GG) contributed to a greater susceptibility to Asthma[18]. In northeastern Iran, Kamiri M., found associations between polymorphisms of the C allele of T1 with severe asthmatic patients and the G allele of nucleotide V4 with moderate asthmatics, respectively (p = 0.006, p = 0.01)[8] and in the study by Foley SC conducted in Canada, the expression of *ADAM33* mRNA was significantly higher in moderate and severe asthma compared to mild asthma (p <0.05) and controls[21] In Indian population it was found that polymorphisms in F + 1, ST + 4, V4 and mutant alleles were significantly associated with an increased risk of asthma (p = 0.031 - <0.001)[22]. In Caracas (Venezuela) it was concluded that the V4 polymorphism is associated with asthma, the G / G genotype being associated with an increased risk of presenting it and C / C with a decreased risk[13]. However, in Asian and Latin American populations the results are contradictory[1,15,23–26], in a meta-analysis about polymorphisms of a Disintegrin and metalloprotease 33 gene (*ADAM33*) and the risk of asthma, significant relationships were reported between asthma and T1, V4, F + 1 and T + 1 polymorphisms in the general population, and in the case of the subgroups analysis by ethnicity, a positive result was only found for polymorphisms T1, V4, F + 1 and T2 in Asia, but no such associations were found in Europe or Latin America, concluding that polymorphisms T1, V4, F + 1, T2 and T + 1 in the ADAM33 gene are risk factors for asthma, especially in the Asian population[15], although Zhu SF demonstrated absence of association for the polymorphism of the ADAM33 gene in Mongolian population[25]. Regarding the Latin American population, Denise L concluded that the *ADAM33* gene is not an important risk factor for asthma or for the phenotypes associated with asthma in Mexicans or Puerto Ricans[26]. In Colombia, Vergara et al. they found no association between the presence of asthma and the polymorphisms of alleles, genotypes and haplotypes of *ADAM33*; and they did not find an association in the subcategories of severe, moderate, or mild asthmatic patients compared to control[23].

Thus, to date, polymorphisms of the *ADAM33* gene have been associated with the presence of asthma in Caucasian, African, Hispanic and Asian populations; however, this information is scarce in the mestizo population and non-existent in the Peruvian population.

Considering that the Peruvian population has great ethnic wealth, in addition to the high prevalence present in the country and the continuous increase in this trend, it is interesting to explore this association. Therefore, the objective of the study was to determine the association between the presence of the V4 polymorphism of the *ADAM33* gene and asthma, and to describe the T1 polymorphism in patients from a hospital in Lambayeque region.

METHODS

Population and sample

A case-control study was developed for the V4 polymorphism, and a descriptive cross-sectional one for the T1. Two groups were compared in the age range between 5-17 years attended by an medical outpatient office of the Almanzor Aguinaga Asenjo-ESSalud Hospital (Hospital III-1) of the Lambayeque department, during the year 2019.

Two groups were compared in the age range between 5-17 years attended by an medical outpatient office of the Almanzor Aguinaga Asenjo-ESSalud Hospital (Hospital III-1) of the Lambayeque department , during the year 2019: the cases were patients diagnosed according to the 2016 Global Initiative for Asthma (GINA) guidelines and those with absence of symptoms due to the use of anti-asthma medications, likewise, patients with asthmatic attacks were excluded; the control subjects did not have a diagnosis of any chronic lung disease or a family history of asthma. In both groups, those buccal swab samples which were no longer viable were excluded.

A simple random sampling was carried out to obtain the cases and controls (V4), and a census study for T1. To estimate the sample size, 23 cases and 23 controls were calculated for the V4 polymorphism, with 6,375 as the expected OR[25]; and for the T1 polymorphism, the sample consisted of all those asthmatic patients who agreed to participate. It was calculated with the OpenEpi software, using a confidence level of 95%, a power of 80%, a ratio of controls per case of 1. Each participant signed an informed consent and assent, and the study was in accordance with the ethical principles of research in human beings consigned in the Declaration of Helsinki and Resolution 8430 of 1993 of the Ministry of Health of Peru. In addition, the study had the approval of the Bioethics Committee of the Faculty of Medicine of the Universidad Católica Santo Toribio de Mogrovejo with Resolution No. 593-2018-USAT-FMED and the Almanzor Aguinaga Asenjo Hospital Ethics Committee.

Sample collection and clinical parameters

Once the consultation was over, the oral swab was performed in the same office, through the invitation made by a pediatric pulmonologist. The buccal cell sample was obtained from the buccal swab with a sterile swab, which was then stored in a sterile 15mL screw cap tube containing 2mL of physiological serum. The samples were transported in a cooler with a cold chain to the Research Laboratory of Universidad Católica Santo Toribio de Mogrovejo, where they were refrigerated until processing.

Through a data collection sheet, patients' general data such as age, sex, origin, duration of the disease, and asthma control were obtained, which was obtained by applying a survey recommended by the GINA that consisted of four questions. The average time for taking the sample and filling in the questionnaire was 10 minutes.

Genomic DNA extraction and genotyping

Genomic DNA was obtained using the PROMEGA Extraction Kit, following the instructions recommended by the manufacturer. The polymorphisms T1 (rs2280091) and V4 (rs2787094) of the *ADAM33* gene were determined by PCR. The amplification mix for a final reaction volume of 20 µl contained 20 ng of genomic DNA and a final concentration of 2.5 µM of magnesium chloride, 200 µM of DNTPs and 1 µM of each primer. The thermal cycler (Biorad, USA) was used under the following temperature conditions: initial denaturation at 95 ° C for 5 minutes, cycles of 95 ° C for 30 seconds, hybridization at 65 ° for 30 seconds and extension at 72 ° for 30 seconds, a final extension of 72 ° for 5 minutes was carried out to later store the amplification products at 4 ° C until their electrophoresis (Table 1). Electrophoresis was carried out in 2% polyacrylamide.

RFLP technique

The amplification products of the T1 genes with 374bp and V4 of 400bp were cut with the NcoI enzymes and Pst1, respectively, the incubation time was 37 ° for 15 hours for the two enzymes in a final volume of 37 ul. Restriction products were observed on 2% polyacrylamide gel and visualized with UV transilluminator.

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Table 1. PCR primers and programs for genotyping ADAM33 by PCR-RFLP.

SNP ID	Gen/SNP primer	Sequence	PCR program
Rs2787094	ADAM33 V4C/G F ADAM33 V4C/G R	5'-ACACACAGAATGGGGGAGAG-3' 5'-CCAGAAGCAAAGGTCACACA-3'	94°C 5 min; 35 ciclos, 94°C 30s, 53°C 30 s, 72°C 30 s; 72°C 5 min
Rs2280091	ADAM33 T1A/G F ADAM33 T1A/G R	5'-ACTCAAGGTGACTGGGTGCT-3' 5'-GAGGGCATGAGGCTCACTTG-3'	94°C 5min; 35 ciclos, 94°C 30s, 54°C 30s, 72°C 30 s; 72°C 5 min

Table 2. Restriction enzymes and length of the digested fragments.

	V4C/G	T1A/G
Restriction enzyme	PstI G: 168+206 C: 374	NcoI A:140+260 G:400

Statistic analysis

Measures of central tendency, especially medians, and of dispersion were calculated to describe the quantitative variables. The qualitative variables were expressed with absolute and relative frequencies.

To determine the association between the V4 polymorphism and the presence of asthma, the Pearson Xi-square test was used, and the OR was subsequently calculated.

The T1 polymorphism was described with absolute and relative frequencies. For all tests a confidence level of 95% was used, and a significance level of 5% or 0.05. SPSS version 25.0 (IBM, New York) software was used for all statistical analyzes.

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Table 3. Demographic and clinical characteristics of cases and controls.

Variable	Cases V4 n (%)	Controls V4 n (%)	P-value	Cases& (T1)
Sex				
Male	17 (65)	13 (50)	-	15 (40)
Female	9	13 (50)	-	23 (60
Age (Med; IQR)	8; 5-10,3	9; 7-11,3	-	9,5; 7-11,3
Origin				
Lambayeque	18 (70)	21 (81)	-	20 (53)
Tumbes	4 (15)	2 (7,5)	-	12 (32)
Cajamarca	2 (7,5)	1 (4)	-	2 (5)
Others	2 (7,5)	2 (7,5)	-	4 (10)
Sick time (Med; RI)	3; 2 – 6,3	-	-	3; 1 – 5,3
Categorized sick time				
1 – 5 years	17 (65)	-	-	26 (69)
> 5 years	7 (27)	-	-	9 (24)
< 1 year	2 (8)	-	-	3 (7)
Asthma control				
Partially controlled	14 (54)	-	-	17 (45)
Well controlled	8 (31)	-	-	16 (42)
Not controlled	4 (15)	-	-	5 (13)
V4				
Negative	14 (54%)	18 (69%)	-	-
Positive	12 (46%)	8 (31%)	-	-
T1				
Negative	-	-	-	5 (13)
Positive	-	-	-	33 (87)

* n = 26 children. Med = median. IQR = interquartile range. & = 38 patients.

RESULTS

Regarding the sociodemographic variables, the global median age was 9 years (IQR: 6 - 11 years), the V4 cases had a median age of 8 (IQR: 5 - 10.3) and the V4 controls had a median 9 years old (IQR: 7 - 11.3). The proportion of male cases was 65% and 40% for V4 and T1, respectively; while in the controls the proportion of men and women was similar (50%).

54% of patients with V4 polymorphism had partially controlled asthma, while patients with T1 polymorphism, 45% were partially controlled and 16% well controlled. In both groups only 15 and 13% were not controlled.

The median time of illness for both the V4 and T1 polymorphism cases was 3 years (IQR: 2 - 6.3 and IQR: 1 - 5.3 years), respectively; Likewise, more than half in both groups (65 and 69% for V4 and T1) had a time of illness that ranged from 1 to 5 years.

Respect to the origin, both groups came mostly from Lambayeque. With respect to the V4 polymorphism, in most cases both cases and controls did not present the polymorphism, I feel positive only in 46% of the cases and 31% of the controls. However, the T1 polymorphism was present in 87% of cases.

When the association between the V4 polymorphism and the presence of asthma was evaluated, the OR was 1.93 (95% CI: 0.62 - 6.00), p value = 0.196 for the Pearson Xi-square test.

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Table 4. Frequency of V4 polymorphism according to sex

V4	Female	Male	Total
Negative	13	19	32
Positive	9	11	20
Total	22	30	52

No differences were found regarding the proportion of men and women with the presence of the mutation. Concerning the total of women, 41% presented the polymorphism, while of the total of men, 37% presented it.

Table 5. Frequency of V4 polymorphism according to Asthma Control.

V4	Well controlled	Not controlled	Partially controlled	Total
Negative (C)	6	2	6	32
Positive (G)	2	2	8	20
Total	8	4	14	52

The ratio of cases with the presence and absence of the factor according to the time of illness remains close to 1: 1. Considering the classification according to the type of asthma control, the proportion of sequences with cytosine and guanine for the patients classified as "uncontrolled" and "partially controlled" remained at 1: 1, except for the case of "well controlled" patients. ", Whose ratio of patients with C to G was 3: 1.

Table 6. Frequency of V4 polymorphism according to origin.

V4	Amazonas	Cajamarca	Lambayeque	Trujillo	Tumbes	Total
Negative	0	2	23	1	6	32
Positive	1	1	16	1	1	20
Total	1	3	39	2	7	52

The ratio of positive to negative factors was approx. 1: 1, except for Tumbes, where the proportion of native people with the mutation is much lower than in other regions. Regarding the total number of patients from Tumbes, only 14% presented the mutation, while in Cajamarca it was 33%, and Lambayeque 41%.

FROM T1

From the 37 patients with asthma who were evaluated for the T1 polymorphism, 87% presented the polymorphism, and only 5 patients did not present it, of them, 3 came from Lambayeque, 3 had well-controlled asthma, 3 were male, and 3 had one to five years of illness.

DISCUSSION

Genetic variations of *ADAM33* can lead to abnormal changes in smooth muscle cells and fibroblasts, which results in hyperresponsiveness and remodeling of the airways, which is correlated with the development of inflammation in the pathogenesis of Asthma[27].

Using a case-control design, no association of individual polymorphisms or V4 haplotypes of the *ADAM33* gene was found with the development of asthma in the pediatric population of the Hospital Almanzor Aguinaga Asenjo. This contrasts with the results of many studies, which found that *ADAM33* polymorphisms and various haplotypes were strongly associated with asthma, predominantly in the Caucasian, Asian and Venezuelan population[8,13,16,20,21,25,27–29]. In the study made by Van Eerdewegh et al., Patients were stratified based on the presence of bronchial hyperresponsiveness, and in the present study, patients were stratified according to the severity of asthma. The same restriction enzymes, amplification sequences, among others, were used respecting a study in a Venezuelan population, which did find an association with the V4 polymorphism in the C / C (OR: 0.14) and G / G (O: 2.10).

Our results suggest that the V4 polymorphism of the *ADAM33* gene would not be an important gene for asthma or for the severity of asthma in our population. The genetic basis of asthma may differ between ethnic groups: a particular subset of polymorphisms of the *ADAM33* gene were identified as risk factors for asthma in Caucasian ethnic groups in the United Kingdom and the United States[14], in the same way, V4 and T1 polymorphisms were identified as risk factors for asthma in a Venezuelan population[11], However, this contrasts with the results of a study carried out in Puerto Rican and Mexican populations in which no such association was evidenced[26].

According to the authors, this is the first study on the analysis of the V4 polymorphism in Peruvian children. Differences in genetic or environmental risk factors may explain the observed differences[30]; however, a deep research is necessary to cover a larger population from other regions, for example, in this study, it was found that asthmatic patients from the Tumbes region presented a much lower proportion of mutation than that of other regions, only 14% compared of Cajamarca and Lambayeque which was 33% and 41%, respectively.

One *ADAM33* variant, the V4 polymorphism, would be related to the splicing of the gene's mRNA, while T1 is related to the elimination of a phosphorylation site important for cell signaling. Modifications in mRNA stability that affect the amount of enzyme secreted may be involved with greater cell turnover and therefore with a greater probability of developing asthma[13]. In a meta-analysis of 29 case-control studies, a general association was found between T1 and the presence of asthma; notwithstanding, when analyzed according to ethnicity, a positive association was found for T1

in the Asian population, but not in the European or Latin American population - only two cases and controls from two countries (Brazil and Colombia) were analyzed 15- This agrees with the absence of association found for the T1 polymorphism and the presence of asthma in the Mexican and Puerto Rican population[26], however, it disagrees with what was found in the Venezuelan population: in the study by Martínez, for T1, an association was found between the presence of the GGAA diploma of *ADAM33* (V4 / T1) and an increased risk of presenting asthma[13].

In the present research, it was found that the frequency of T1 polymorphism was high in asthmatic patients at the Hospital Almanzor Aguinaga Asenjo-ESSalud (87%), yet, it is recommended to study the frequency of said polymorphism also in controls, so that it can be determine the association level. These results are particularly important to Peru due to the high prevalence of asthma, the high morbidity and mortality in this population[2,4,6]. Identification of specific ethnic and environmental genetic risk factors for asthma allows understanding the mechanisms and developing more effective and specific therapies for these populations.

CONCLUSION

There is no association between the V4 polymorphism and the presence of asthma in pediatric patients from a hospital in Lambayeque; however, T1 polymorphism occurs with high frequency (87%) in asthmatic patients at the Hospital Almanzor Aguinaga Asenjo - ESSalud.

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BIBLIOGRAPHIC REFERENCES

1. Bijanzadeh M, Mahesh PA, Ramachandra NB. An understanding of the genetic basis of asthma [Internet]. Vol. 134, Indian Journal of Medical Research. Wolters Kluwer -- Medknow Publications; 2011 [citado 10 de septiembre de 2020]. p. 149-61. Disponible en: /pmc/articles/PMC3181014/?report=abstract

2. Viviana Lezana JCA. Consideraciones epidemiológicas del asma en Latinoamérica [Internet]. Neumología Pediátrica. 2017 [citado 13 de octubre de 2020]. p. 45-8. Disponible en: http://www.neumologia-pediatrica.cl/wp-content/uploads/2017/06/Consideraciones.pdf

3. Huerta López JG, Jiménez Gutiérrez C, Diana Regina Gómez García D, Martha Gabriela Tavera Rodríguez D, Manuel López Andrade J. Evaluación de la calidad clínica y metodológica de las guías de práctica clínica para el manejo del asma en pacientes pediátricos [Internet]. Vol. 20, Núm. 1 • Enero-Abril. Medigraphic; 2011 [citado 13 de octubre de 2020]. Disponible en: www.medigraphic.org.mx

4. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet [Internet]. 26 de agosto de 2006 [citado 13 de octubre de 2020];368(9537):733-43. Disponible en: http://www.thelancet.com/article/S0140673606692830/fulltext

5. Munayco C V, Arana J, Torres-Chang J, Saravia L, Soto-Cabezas G. Prevalencia y factores asociados al asma en niños de 5 a 14 años de un Área Rural del Sur del Perú. Vol. 26, Rev Peru Med Exp Salud Publica. 2009.

6. Gerencia Regional de Salud. Boletín informativo/asma [Internet]. 2018 [citado 13 de octubre de 2020]. Disponible en: https://www.regionlambayeque.gob.pe/web/?pass=NA==

7. Global Strategy for Asthma Management and Prevention Revised 2006 [Internet]. 2006 [citado 6 de febrero de 2021]. Disponible en: www.ginasthma.org.

8. Zand Karimi MR, Faridhosseini R, Abbaszadegan MR, Jabbari Azad F, Shirkani A, Riyahi A, et al. Association of ADAM33 gene polymorphisms with allergic asthma. Iran J Basic Med Sci. 2014;17(9):716-21.

9. Asher MI. Worldwide variations in the prevalence of asthma symptoms: The International Study of Asthma and Allergies in Childhood (ISAAC). Eur Respir J [Internet]. 1998 [citado 10 de septiembre de 2020];12(2):315-35. Disponible en: https://pubmed.ncbi.nlm.nih.gov/9727780/

10. Gupta A, Chakraborty S, Agrawal A. Molecular and genomic basis of bronchial asthma. En: Clinical Molecular Medicine. Elsevier; 2020. p. 353-66.

11. Modena BD, Doroudchi A, Patel P, Sathish V. Leveraging genomics to uncover the genetic, environmental and age-related factors leading to asthma. En: Genomic and Precision Medicine: Infectious and Inflammatory Disease. Elsevier; 2019. p. 331-81.

12. Ortiz RA, Barnes KC. Genetics of Allergic Diseases [Internet]. Vol. 35, Immunology and Allergy Clinics of North America. W.B. Saunders; 2015 [citado 13 de octubre de 2020]. p. 19-44. Disponible en: /pmc/articles/PMC4415518/?report=abstract

13. Martínez D, Lema D, Del D, Moreno C, García AH, Garmendia JV, et al. Polimorfismos de nucleótidos simples V4 y T1 del gen ADAM33 en pacientes venezola-nos con asma o enfermedad pulmonar obstructiva crónica. Invest Clin [Internet]. 2016;57(2):176-86. Disponible en: http://www.scielo.org.ve/pdf/ic/v57n2/art06.pdf

14. Zheng W, Wang L, Su X, Hu XF. Association between V4 polymorphism in the ADAM33 gene and asthma risk: A meta-analysis. Genet Mol Res [Internet]. 6 de febrero de 2015 [citado 13 de octubre de 2020];14(1):989-99. Disponible en: https://pubmed.ncbi.nlm.nih.gov/25730038/

15. Liang S, Wei X, Gong C, Wei J, Chen Z, Deng J. A disintegrin and metalloprotease 33 (ADAM33) gene polymorphisms and the risk of asthma: A meta-analysis [Internet]. Vol. 74, Human Immunology. Hum Immunol; 2013 [citado 13 de octubre de 2020]. p. 648-57. Disponible en: https://pubmed.ncbi.nlm.nih.gov/23380143/

16. Van Eerdewegh P, Little RD, Dupuis J, Del Mastro RG, Falls K, Simon J, et al. Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. Nature [Internet]. 25 de julio de 2002 [citado 13 de octubre de 2020];418(6896):426-30. Disponible en: https://pubmed.ncbi.nlm.nih.gov/12110844/

17. Van Diemen CC, Postma DS, Vonk JM, Bruinenberg M, Scheuten JP, Boezen HM. A disintegrin and metalloprotease 33 polymorphisms and lung function decline in the general population [Internet]. Vol. 172, American Journal of Respiratory and Critical Care Medicine. Am J Respir Crit Care Med; 2005 [citado 13 de octubre de 2020]. p. 329-33. Disponible en: https://pubmed.ncbi.nlm.nih.gov/15879414/

18. Wang J, Simayi M, Wushouer Q, Xia Y, He Y, Yan F, et al. Association between polymorphisms in ADAM33, CD14, and TLR4 with asthma in the Uygur population in China. Genet Mol Res [Internet]. 18 de junio de 2014 [citado 13 de octubre de 2020];13(2):4680-90. Disponible en: https://pubmed.ncbi.nlm.nih.gov/25036518/

19. Howard TD, Postma DS, Jongepier H, Moore WC, Koppelman GH, Zheng SL, et al. Association of a disintegrin and metalloprotease 33 (ADAM33) gene with asthma in ethnically diverse populations. J Allergy Clin Immunol [Internet]. 1 de octubre de 2003 [citado 13 de octubre de 2020];112(4):717-22. Disponible en: https://pubmed.ncbi.nlm.nih.gov/14564349/

20. Li HF, Yan LP, Wang K, Li XT, Liu HX, Tan W. Association between ADAM33 polymorphisms and asthma risk: A systematic review and meta-analysis [Internet]. Vol. 20, Respiratory Research. BioMed Central Ltd.; 2019 [citado 10 de septiembre de 2020]. Disponible en: /pmc/articles/PMC6385425/?report=abstract

21. Foley SC, Mogas AK, Olivenstein R, Fiset PO, Chakir J, Bourbeau J, et al. Increased expression of ADAM33 and ADAM8 with disease progression in asthma. J Allergy Clin Immunol [Internet]. abril de 2007 [citado 10 de septiembre de 2020];119(4):863-71. Disponible en: https://pubmed.ncbi.nlm.nih.gov/17339047/

22. Awasthi S, Tripathi P, Ganesh S, Husain N. Association of ADAM33 gene polymorphisms with asthma in Indian children. J Hum Genet [Internet]. marzo de 2011 [citado 13 de octubre de 2020];56(3):188-95. Disponible en: https://pubmed.ncbi.nlm.nih.gov/21179102/

23. Vergara CI, Acevedo N, Jiménez S, Martínez B, Mercado D, Gusmão L, et al. A Six-SNP Haplotype of <i>ADAM33 </i>Is Associated with Asthma in a Population of Cartagena, Colombia. Int Arch Allergy Immunol [Internet]. abril de 2010 [citado 10 de septiembre de 2020];152(1):32-40. Disponible en: https://www.karger.com/Article/FullText/260081

24. Deng R, Zhao F, Zhong X. T1 polymorphism in a disintegrin and metalloproteinase 33 (ADAM33) gene may contribute to the risk of childhood asthma in Asians. Inflamm Res [Internet]. 1 de mayo de 2017 [citado 13 de octubre de 2020];66(5):413-24. Disponible en: https://pubmed.ncbi.nlm.nih.gov/28285393/

25. Zhu S, Li J. Association between polymorphism of ADAM33 gene and bronchial asthma in Mongolian population. Natl Med J China [Internet]. 20 de septiembre de 2016 [citado 10 de septiembre de 2020];96(35):2791-5. Disponible en: https://europepmc.org/article/med/27686544

26. Lind DL, Choudhry S, Ung N, Ziv E, Avila PC, Salari K, et al. ADAM33 Is Not Associated with Asthma in Puerto Rican or Mexican Populations. Am J Respir Crit Care Med [Internet]. 1 de diciembre de 2003 [citado 10 de septiembre de 2020];168(11):1312-6. Disponible en: https://pubmed.ncbi.nlm.nih.gov/12958057/

27. Sun FJ, Zou LY, Tong DM, Lu XY, Li J, Deng CB. Association between ADAM metallopeptidase domain 33 gene polymorphism and risk of childhood asthma: A meta-analysis. Brazilian J Med Biol Res [Internet]. 2017 [citado 9 de septiembre de 2020];50(10). Disponible en: /pmc/articles/PMC5579965/?report=abstract

28. Sabar MF, Ghani MU, Shahid M, Sumrin A, Ali A, Akram M, et al. Genetic variants of ADAM33 are abociated with asthma susceptibility in the Punjabi population of Pakistan. J Asthma [Internet]. 20 de abril de 2016 [citado 9 de septiembre de 2020];53(4):341-8. Disponible en: https://pubmed.ncbi.nlm.nih.gov/26666372/

29. Shen B, Lin R, Wang CC, Rei J, Sun Y, Yang Y Le, et al. ADAM33 gene polymorphisms identified to be associated with asthma in a Chinese Li population. Biomed Reports [Internet]. 1 de marzo de 2017 [citado 9 de septiembre de 2020];6(3):323-8. Disponible en: https://pubmed.ncbi.nlm.nih.gov/28451394/

30. González Burchard E, Ziv E, Coyle N, Gomez SL, Tang H, Karter AJ, et al. The importance of race and ethnic background in biomedical research and clinical practice [Internet]. Vol. 348, New England Journal of Medicine. N Engl J Med; 2003 [citado 13 de octubre de 2020]. p. 1170-5. Disponible en: https://pubmed.ncbi.nlm.nih.gov/12646676/