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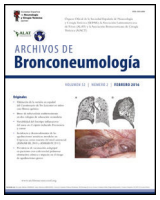

Scientific Letter

Genome-wide Association Study of Asthma Exacerbations in the Spanish Population

To the Director,

Asthma is a complex respiratory disease characterized by chronic airway inflammation leading to respiratory symptoms, such as wheezing, coughing, shortness of breath, and airflow limitation.[1] According to the last global reports, asthma affected 300 million individuals worldwide in 2019, and caused 400,000 annual deaths.[2] However, large differences in asthma prevalence across populations and regions are observed, even within the same country, as in Spain.[3] Some patients may not respond appropriately to the treatment with controller medications, and their worsened symptoms can lead to life-threatening episodes known as asthma exacerbations (AEs).[1] In recent years, several single-nucleotide polymorphisms (SNPs) associated with AEs have been identified through genome-wide association studies (GWAS).[4] These studies uncovered genetic biomarkers of AE with population-specific effects or shared across populations, such as Europeans, African Americans, and Hispanic/Latin Americans.[4] To the best of our knowledge, no prior study has focused on the association of genetic variants with AEs in the Spanish population. Therefore, this study aimed to identify specific genetic variants associated with AEs in the Spanish population.

A discovery and replication design was followed. The discovery included 345 adults from the *Genomics and Metagenomics of Asthma Severity* (GEMAS),[5] 369 from *Characterizing Alpha-1-Antitrypsin Deficiency in patients with pulmonary diseases* (CAATDPUL),[6] and 138 from *MEchanisms involved in the Genesis and evolution of Asthma* (MEGA)[7] studies (Table 1). The replication phase analyzed 90 children with asthma enrolled in the GEMAS study. Asthma patients were classified into cases and controls based on the presence or absence of severe AEs, respectively, defined by the presence of hospitalizations, emergency room visits, and/or oral corticosteroid use in the past 12 months. Genotyping data was available for the CAATDPUL and MEGA studies,[6] and was newly generated for some of the GEMAS participants (Table E1, supplementary material). Association between genetic variants and AEs was assessed using logistic regression models adjusted by age, sex, and principal components capturing genetic ancestry estimated from the genotype matrix using PLINK 2.0. In the discovery phase, GWAS for AEs was conducted separately for each study, followed by a meta-analysis. From the suggestive variants (p-value $<5\times10^{-5}$), independent variants ($r^2 \leq 0.8$) within 1 Megabase were further explored for replication, which was declared for variants showing nominal association (p-value ≤ 0.05) and consistent effects with the ones found in the discovery phase. To ensure the robustness of the replicated associations, sensitivity analyses were performed by further adjusting the logistic regression models for additional potential confounders, such as obesity, body mass index (BMI) categories, smoking, and asthma severity. Additionally, we assessed the effects of the SNPs with evidence of replication on DNA methylation (DNAm) through a cis-methylation quantitative trait locus (meQTL) analysis. *In silico* confirmation of functional effects on DNAm (meQTLs) and gene expression (eQTLs) was evaluated using public data. Finally, a Gene-Set Enrichment Analysis (GSEA) was carried out to evaluate previous gene-trait and gene-drug target associations. Detailed methods are provided in the supplementary material.

From the 8.7 million SNPs included in the meta-analysis from the discovery stage, 193 SNPs showed suggestive association with AEs (Fig. 1A, Table E2, supplementary material), including 52 independent variants (Table E3). The most significant association was the SNP rs4759090 annotated to the *PDE1B* gene (odds ratio G allele = 0.56, 95% confidence interval = 0.43–0.71, p-value = 2.90×10^{-6}) (Fig. E2, supplementary material). From the 52 SNPs independently associated with AEs, three were nominally replicated (p-value <0.05) in the peditric population: rs847517 (BRMS1L), rs79017090 (ZNF780A), and rs11786009 (DUSP4), Table E4, supplementary material, Fig. 1B). After sensitivity analyses, the association of these three SNPs was robust to the adjustment for all potential confounders evaluated (Table E5, supplementary material).

Among the replicated associations, the SNPs rs79017090 and rs847517 were significantly associated with DNAm levels at six and two CpGs, respectively (Table E6, supplementary material). *In silico* analyses revealed that the G allele of the SNP rs79017090 showed a significant association with increased *ZNF780A* gene expression in whole blood (coefficient = 0.20; p-value = 1.60×10^{-11}) and lung tissue (coefficient = 0.46; p-value = 1.40×10^{-24}). Finally, the GSEA showed an enrichment in previous trait-associations, including cholesterol levels, BMI, and life expectancy, and also in drugs acting as phosphodiesterase inhibitors (*i.e.*, oxagrelate, and papaverine) (FDR <0.05) (Fig. E3, Table E7, supplementary material).

To the best of our knowledge, this is the first GWAS of AEs specifically focused on the Spanish population, reporting novel associations with AEs not revealed by the largest meta-GWAS of AEs performed to date.[8] In the meta-analysis of 852 adults with asthma, the most significant association with AEs was the SNP rs4759090, located at the second intronic region of a member of the cyclic nucleotide phosphodiesterase family (*PDE1B*) gene. PDE1B acts by hydrolyzing second messengers regulating smooth muscle relaxation in asthma and participates in interleukin-13 (IL-13) production, which is involved in allergic lung inflammation.[9] In fact, PDE inhibitors such as theophylline are

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Table 1
Demographic and Clinical Characteristics of the Studies Included in the Discovery and Replication Phases.

Characteristics	Discovery Phase – Adults						Replication Phase – Children	
	N	CAATDPUL	*N*	GEMAS	*N*	MEGA	*N*	GEMAS
Age (years)	369	45.0 (31.0–63.0)	345	45.0 (28.0–56.8)	138	47.0 (38.0–58.8)	90	11.0 (9.0–12.0)
Sex (female)	369	249 (67.5)	345	228 (65.9)	138	98 (71.0)	90	36 (40.0)
Asthma exacerbations	369	138 (37.4)	345	160 (46.4)	138	48 (34.8)	90	53 (58.9)
OCS use		NA		122 (35.4)		20 (14.5)		52 (57.8)
ER visits		NA		134 (38.8)		39 (28.3)		34 (37.8)
Hospitalizations		13 (3.5)		28 (8.1)		12 (8.7)		10 (11.1)
IgE levels (UI/ml)	311	95.9 (34.2–278.4)	300	157.0 (55.1–543.0)	127	171.0 (69.6–412.5)	29	700.0 (355.0–1943.0)
Eosinophil counts (cells/μl)	369	300.0 (200.0–400.0)	318	300.0 (140.0–500.0)	136	300.0 (200.0–500.0)	34	640.0 (457.5–950.0)
Pulmonary function[a]								
FEV_1 (% predicted)	367	93.5 (82.1–103.0)	237	87.1 (73.1–97.0)	136	89.0 (73.7–102.9)	84	97.8 (89.2–105.2)
FVC (% predicted)	367	95.0 (85.3–104.0)	234	91.5 (80.6–101.9)	136	101.0 (87.67–111.7)	84	100.8 (92.1–108.7)
FEV_1/FVC (% predicted)	367	80.5 (73.1–85.5)	237	77.2 (70.4–83.3)	136	87.4 (80.9–96.4)	84	85.2 (79.9–89.2)
Well-controlled asthma[b]	368	199 (54.1)	227	91 (39.9)	137	96 (70.1)	84	66 (78.6)
BMI categories	367		328		134		85	
Thinness		4 (1.1)		2 (0.6)		4 (3.0)		2 (2.4)
Normal weight		114 (31.0)		101 (30.7)		54 (40.3)		55 (64.7)
Overweight		99 (27.0)		114 (34.7)		49 (36.6)		17 (20.0)
Obesity		150 (40.9)		112 (34.0)		27 (20.1)		11 (12.9)
Asthma severity[*]	369		301		138		87	
Mild		189 (51.2)		4 (1.3)		44 (31.9)		5 (5.7)
Moderate		165 (44.7)		22 (7.3)		41 (29.7)		9 (10.3)
Severe		15 (4.1)		276 (91.4)		53 (38.4)		73 (83.9)
Ever-smoking	369	117 (31.7)	341	111 (32.5)	138	58 (42.0)	90	0 (0)

Descriptive statistics are represented as medians (interquartile range) for continuous variables and counts (proportions) for categorical variables. *Abbreviations*: BMI: body mass index; CAATDPUL: Characterizing Alpha-1-Antitrypsin Deficiency in patients with pulmonary diseases; ER: emergency visits; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; GEMAS: Genomics and Metagenomics of Asthma Severity; IgE: immunoglobulin E; MEGA: MEchanisms involved in the Genesis and evolution of Asthma; *N*: sample size; NA: not available; OCS: oral corticosteroids use.

[a] Predicted values of lung function measurements were estimated using the Global Lung Function Initiative (GLI) 2012 equations.

[b] Asthma control was assessed by the asthma control questionnaire (ACQ) score in GEMAS and by the asthma control test (ACT) score in CAATDPUL and MEGA.

[*] Severity was estimated using treatment steps adapted from the Global Initiative for Asthma (GINA) guidelines 2020. For CAATDPUL and MEGA severity was evaluated through the Spanish Guide for the Management of Asthma (GEMA) guidelines.

effective drugs in asthma treatment due to their anti-inflammatory effect.[9]

Regarding the validated associations, the G allele of the SNP rs79017090, located at the intergenic region of the Zinc Finger Protein 780A (*ZNF780A*) and Mitogen-Activated Protein Kinase Kinase Kinase 10 (*MAP3K10*) genes, showed a risk effect for developing AEs and exhibited an association with DNAm at several nearby CpG sites in whole blood from adults with asthma. Moreover, *in silico* analyses revealed an association of the same allele with increased *ZNF780A* expression in whole blood and lung tissue. Epigenetic variation in the *ZNF780A* gene, has been previously associated with prenatal exposure to perfluorononanoic acid,[10] a compound associated with childhood asthma risk in the Spanish population.[11] On the other hand, MAP3K10 participates in the MAPK signaling pathway that contributes to the airway inflammation and remodeling processes underlying asthma.[12] In addition, the T allele of SNP rs847517 (*BRMS1L*) and the G allele of SNP rs11786009 (*DUSP4*) showed a consistent protective effect against AEs in both adults and children with asthma. *BRMS1L*, which encodes a breast cancer metastasis-suppressor, is involved in Wnt signaling[13] epigenetic regulation, a pathway previously linked to AEs despite corticosteroid use.[14] *DUSP4* encodes a protein from the dual specificity phosphatase subfamily which deactivates kinases in the MAPK pathway, reducing inflammation and enhancing corticosteroids' anti-inflammatory effects, thereby improving corticosteroid sensitivity.[15] Notably, a previous study showed *DUSP4* expression was lower in blood from patients with severe asthma, suggesting it as a potential therapeutic target.[15]

Finally, genetic variants related to AEs were enriched in previous associations reported for BMI, cholesterol, and life expectancy. Obesity and abnormal levels of lipids in blood (dyslipidemia), including cholesterol, have been shown to increase the frequency and severity of AEs.[16,17] Moreover, previous studies have reported that AEs lead to a higher mortality risk in the next month.[18] Focusing on drugs, we found evidence of enrichment in PDE inhibitors, such as oxagrelate and papaverine. Although no major studies have validated these enriched drugs as a primary asthma treatment, other PDE inhibitors as theophylline are commonly used as second-line drugs for asthma.[19]

This study has several strengths. First, the definition of AEs was consistent across all studies comprised in the discovery and replication phases. Second, despite the small sample size, three suggestive associations were replicated and showed consistent effects in the pediatric population. Moreover, these associations were robust to the adjustment for potential confounders of AEs. Third, we integrated epigenomic and genomic data from our studies, as well as *in silico* data from transcriptomics and genomics, to assess the potential functional role of the associated variants on DNAm and gene expression levels.

On the other hand, we acknowledge some study limitations. First, AEs definition was based on retrospective questionnaires in the discovery and replication phases, which could reduce the accuracy and reliability of the phenotype, compromising the ability to detect robust genetic associations. Second, the reduced statistical power given by the limited sample size analyzed could explain the inability of our associations to reach the genome-wide significance threshold. Moreover, AEs constitute a complex and heterogeneous phenotype, and it has been shown that large sample sizes are necessary for the detection of any genome-wide signal in such scenario.[20] Third, our discovery was focused on adults and the replication in

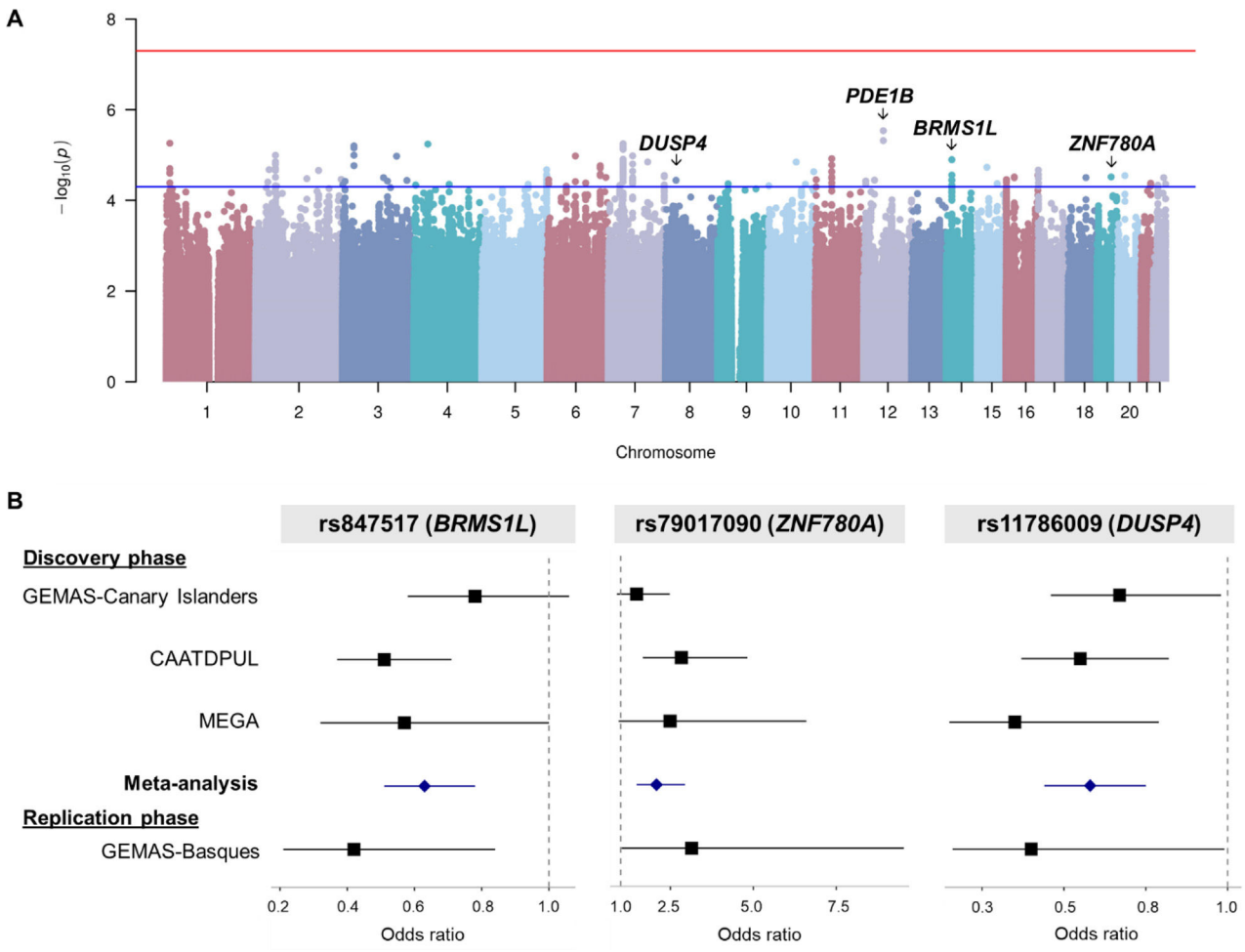

Fig. 1. (A) Manhattan plot of the meta-GWAS of asthma exacerbations in the discovery phase. The blue and red lines represent the suggestive (p-value $<5 \times 10^{-5}$) and the genome-wide (p-value $<5 \times 10^{-8}$) significance thresholds, respectively. Gene annotation is represented for the top-hit signal and those with evidence of replication. (B) Forest plot of the association results for the SNPs rs11786009 (*DUSP4*), rs79017090 (*ZNF780A*), and rs847517 (*BRMS1L*) from the meta-GWAS of asthma exacerbations in the discovery phase and replication phase. The *x*-axis represents the odds ratios (ORs) and the vertical line corresponds to OR = 1, which means no significant effect. ORs and confidence intervals obtained from SNP-AEs association in each study and meta-analysis are represented as squares and lines or diamonds and lines, respectively.

children, which limited our ability to fully replicate the results found in the initial phase. Fourth, the functional implication of our AEs' suggestive associations on gene expression was explored using publicly available from European populations since gene expression data was not available in the analyzed cohorts.

In summary, the first GWAS of AEs conducted in the Spanish population revealed novel associations for genetic loci with AEs with consistent effects across age groups. We also reported that some of these loci regulate DNAm levels at nearby CpG sites and gene expression in whole blood and lung. The AEs-related genetic markers were enriched in BMI, cholesterol, and life expectancy. These findings provide novel insights into the molecular mechanisms of AEs and suggest potential alternative therapies. However, future investigation of the genetic basis underlying AEs in larger sample sizes is needed.

CRediT Authorship Contribution Statement

MP-Y was involved in the conceptualization and design of the study; RG-P, JV, FL-D, and MP-Y in funding acquisition; RG-P, OS, JMH-P, JAP-P, MAG-C, PP-G, IS-M, EM-L, PC, LL-F, BR-B, LMG-G, MJC, FJG-B, CM-R, JM, XM, JMO, VP, SQ, AV, JS, and VP in data acquisition; EM-G, JP-G, MM-A, FL-D, and MP-Y in data curation, formal analysis, and/or interpretation of the data; MP-Y in the project supervision. EM-G and MP-Y participated in the preparation and writing of the original draft. All authors were involved in revising the manuscript and approving the final version. All authors have read and agreed to the published version of the manuscript.

Declaration of Generative AI and AI-assisted Technologies in the Writing Process

The authors declare that none of the material has been produced with the help of any artificial intelligence software or tool.

Role of the Funding Source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

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Declaration of Competing Interests

EM-G reports a fellowship from the Canarian Agency for Research, Innovation, and the Information Society of the Counseling of Universities, Science and Innovation and Culture. JP-G reports a fellowship from the MICIU. MM-A reports a fellowship from the Canarian Agency for Research, Innovation and the Information Society of the Counseling of Universities, Science and Innovation and Culture and from the MICIU. RG-P reports grants from Fundación Canaria Instituto de Investigación Sanitaria de Canarias (FIISC) (grant PIFIISC22/24) and from Sociedad Española de Alergología e Inmunología Clínica (SEAIC). JMH-P reported grant 1264-2022 from Sociedad Española de Neumología y Cirugía Torácica (SEPAR http://www.separ.es). JV and MP-Y report grants from the Instituto de Salud Carlos III, Madrid, Spain. MP-Y reports grants from the Spanish Ministry of Science, Innovation, and Universities (MICIU/AEI/10.13039/501100011033). MP-Y also received grant support from CSL Behring (A23100219) and lecture fees from AstraZeneca. The rest of the authors declare they have no competing interests or other interests that might be perceived to influence the interpretation of the article. No supporting institution may gain or lose financially through this publication.

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Data Availability

All data necessary to evaluate the conclusions of this manuscript are reported in the main text and/or the supplementary information. The summary statistics of the full genome-wide association study will be available at the Zenodo repository (DOI: 10.5281/zenodo.14857204).

Appendix A. Supplementary Data

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.arbres.2025.03.012.

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