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A genome-wide association study of severe asthma exacerbations in Latino children and adolescents

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METHODS

Study populations included in the meta-analysis of GWAS of severe exacerbations

Hartford-Puerto Rico study (HPR): From September 2003 to June 2010, children with and without asthma were recruited in Hartford, (CT) and San Juan (PR), as reported elsewhere [1]; only children with asthma (n=618) were considered for the current analysis. All participants were 6 to 14 years old and had four Puerto Rican grandparents, and asthma was defined as physician-diagnosed asthma and ≥1 episode of wheeze in the prior year. Genome-wide genotyping was conducted using the HumanOmni2.5 BeadChip platform (Illumina Inc., San Diego, CA), as previously described [2]. Genotype imputation was performed with the Michigan Imputation Server [3], using the Haplotype Reference Consortium (HRC) r1.1 2016 [4] as the reference panel. Genotyped or imputed SNPs with imputation quality r^2 <0.3 or Hardy-Weinberg equilibrium (HWE) P <1×10^{-4} or minor allele frequency MAF <0.05 were excluded from the analysis. Written parental consent was obtained for participating children, from whom written assent was also obtained. The study was approved by the Institutional Review Boards of the University of Puerto Rico (San Juan, PR), Brigham and Women's Hospital (Boston, MA) and the University of Pittsburgh (Pittsburgh, PA).

The Genetics of Asthma in Latino Americans study (GALA II): Subjects were recruited using a combination of community and clinic-based approaches from centers throughout the U.S. (Chicago [IL], Bronx [NY], Houston [TX], San Francisco Bay Area [CA] and Puerto Rico). Subjects were eligible if they were aged 8 to 21 years, had <10 pack-years of smoking history and were not current smokers, and had four grandparents of Hispanic or Latino ethnicity. Asthma was defined based on a physician's diagnosis and self-reported symptoms and medication use for asthma within the last two years. Genotyping was conducted with the Axiom® LAT1 array (World Array 4, Affymetrix, Santa Clara, CA), and QC was performed as previously described [5].

Imputation was performed using the Michigan Imputation Server [3], using HRC r1.1 2016 [4] as reference, and only SNPs with MAF ≥0.05 and imputation quality r^2≥0.3 were kept. The study was approved by the Institutional Review Boards of UCSF and at each participating center. All subjects and their parents provided written informed assent and written informed consent, respectively.

The Genetics of Asthma in Costa Rica Study (GACRS): Subject recruitment and study procedures in the GACRS have been described elsewhere [6, 7]. In brief, Costa Rican children ages 6 to 14 years were recruited from February 2001 to July 2011. Children were included in the study if they had asthma (defined as physician-diagnosed asthma and at least two respiratory symptoms [wheezing, cough, or dyspnea] or a history of asthma attacks in the previous year) and a high probability of having at least 6 great-grandparents born in the Central Valley of Costa Rica. Genome-wide genotyping was conducted using the HumanOmniExpress-12v1_A chip [6]. Genotype imputation was performed with the Michigan Imputation Server [3], using the Haplotype Reference Consortium (HRC) r1.1 2016 [4] as the reference panel, with QC measures as in the HPR study. In addition, since the original data were for nuclear families, SNPs with Mendelian error rate ≥0.01 were excluded from the analysis. The study was approved by the Institutional Review Boards of the Hospital Nacional de Niños (San Jose, Costa Rica) and Brigham and Women's Hospital (Boston, Mass).

The Social Changes, Asthma and Allergy in Latin America study (SCAALA) – Bahia, Brazil: Children ages 5 to 12 years were recruited in 2005. Subject recruitment and the study protocol have been described in detail [8]. Genotyping was carried out using the Illumina HumanOmni2.5-8v1 Kit BeadChip (Illumina, San Diego, CA) platform. QC measures for the genotypic data were similar to those in the HPR study. Written informed consent was obtained from the legal guardian

of each subject. The study was approved by the ethics committees at the Federal University of Bahia and National Council for Ethics in Research.

Study populations included in molecular quantitative trait analyses in nasal epithelium

The Epigenetic Variation and childhood Asthma in Puerto Rico study (EVA-PR): In EVA-PR, children with and without asthma (aged 9-20 years) were recruited in San Juan (PR) from February 2014 to May 2017, using a similar approach to that used in the HPR study [9]. DNA and RNA were extracted from nasal specimens collected from the inferior turbinate, as reported elsewhere [9]. For whole-genome methylation QC, the R package *ENmix* was used to filter CpG probes with obvious multimodal distributions [10]. Cross-reactive and SNP-containing probes [11], sex chromosomal probes, and low-quality probes (>10% of samples with detection p-values >0.01) were removed. We further removed CpG probes with mean β-value <0.1 or >0.9 [12]. Methylation β-values were calculated as a percentage: $\beta=M/(M+U+\alpha)$, where M and U represent methylated and unmethylated signal intensities, respectively, and α is an arbitrary offset to stabilize β-values where fluorescent intensities are low. β-values were then transformed to M-values as $\log_2(\beta/(1-\beta))$. For RNA-Seq QC, FastQC was used to check read quality in raw fastq files [13]. Low quality reads and 3' adapters were trimmed with Trim Galore! and Cutadapt [14, 15]. Saved reads were aligned to reference human genome (hg19) with STAR [16] and TPM (Transcripts Per Kilobase Million) was used as proxy for gene expression level. Samples with low alignment percentage were removed from downstream analyses. Furthermore, low expressed genes with mean TPM <0.5 were removed. The study was approved by the institutional review boards of the University of Puerto Rico (San Juan, PR) and the University of Pittsburgh (Pittsburgh, PA). Written parental consent and assent were obtained from participants <18 years old, and consent was obtained from participants ≥18 years old.

PIAMA: Details of the study design and protocol have been previously published [17, 18]. The Medical Ethical Committees of the participating institutes approved the study, and the parents and legal guardians of all participants, as well as the participants themselves, gave written informed consent. At the age of 16 years, nasal epithelial cells were collected at two study centers (Groningen and Utrecht) [19] by brushing the lateral area underneath the right inferior turbinate. DNA methylation data were pre-processed with Bioconductor package *minfi* [20], using the original IDAT files from the HiScanSQ scanner. Samples with call rate <99% were removed. 65 SNP probes were used to check for concordance between paired DNA samples (nasal and blood DNA samples from the same subjects were hybridized in the same experiments); paired samples with Pearson correlation coefficient <0.9 were excluded, as were probes on sex chromosomes, probes that mapped to multiple loci, 65 SNP-probes, and probes containing SNPs at the target CpG sites with a MAF>0.05 [11]. "DASEN" [21] was used to perform signal correction and normalization. After QC, 455 samples and 436 824 probes remained, and 432 samples had matched genotype data.

Meta-analysis of GWAS of SAEs

METAL [22] takes *P*-values across independent studies as input, with MAF, sample size and effect direction considered. After the test allele was determined, a Z-score was calculated in each study:

$$Z_i = \Phi^{-1}\left(1 - {}^{P_i}/_{2}\right) \times \mathrm{sign}(\Delta_i),$$

where Z_i is the Z-score for study *i*, P_i is the *P*-value for study *i*, Δ_i is the direction of effect for study *i*, and Φ^{-1} gives the percentile of a standard normal distribution. Then, the meta Z-score and *P*-value can be calculated,

$$Z = \frac{\sum_i Z_i w_i}{\sqrt{\sum_i w_i^2}}, \qquad P = 2\Phi(|-Z|)$$

where Z is the meta Z-score, P is the meta *P*-value, and w_i is the weight for study *i*,

$$w_i = \frac{MAF_i(1 - MAF_i)N_i^{cas}N_i^{con}}{(N_i^{cas} + N_i^{con})}$$

where MAF_i is the minor allele frequency for study *i*, N_i^{cas} is the number of cases for study *i* and N_i^{con} is the number of controls for study *i*. This weighting is intended to assign larger weights to studies with larger sample size, more balanced case-control numbers and higher MAF [23]. Summary odds ratios (ORs) were calculated by averaging the study-specific log-odds ratios, with weights reflecting the standard errors from the study-specific ORs. Specifically,

$$\mathrm{OR} = exp\left(\sum_i \frac{log(\mathrm{OR}_i)}{(\mathrm{SE}_i)^2} \Big/ \sum_i \frac{1}{(\mathrm{SE}_i)^2}\right)$$

where SE_i is the standard error of log(OR) for study *i*.

Higgin's & Thompson's I^2

We first need to calculate Cochran's *Q*-statistic, which is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method.

$$Q = \sum_i \frac{1}{(\mathrm{SE}_i)^2}\left(log(\mathrm{OR}_i) - \sum_i \frac{log(\mathrm{OR}_i)}{(\mathrm{SE}_i)^2} \Big/ \sum_i \frac{1}{(\mathrm{SE}_i)^2}\right)^2$$

where SE_i is the standard error of log(OR) for study *i*. We then calculated I^2 by using

$$I^2 = max\left\{0, \quad \frac{Q - (K - 1)}{Q}\right\}$$

where *K* is the number of studies, which is 4.

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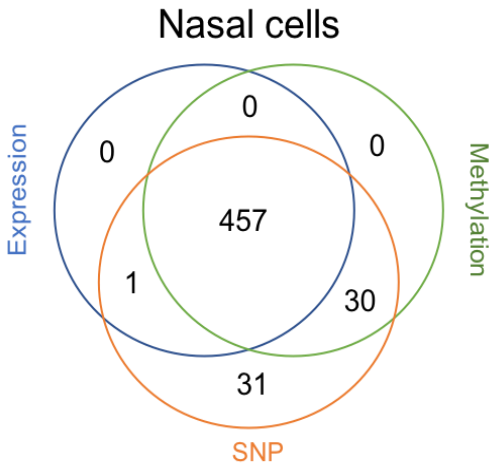
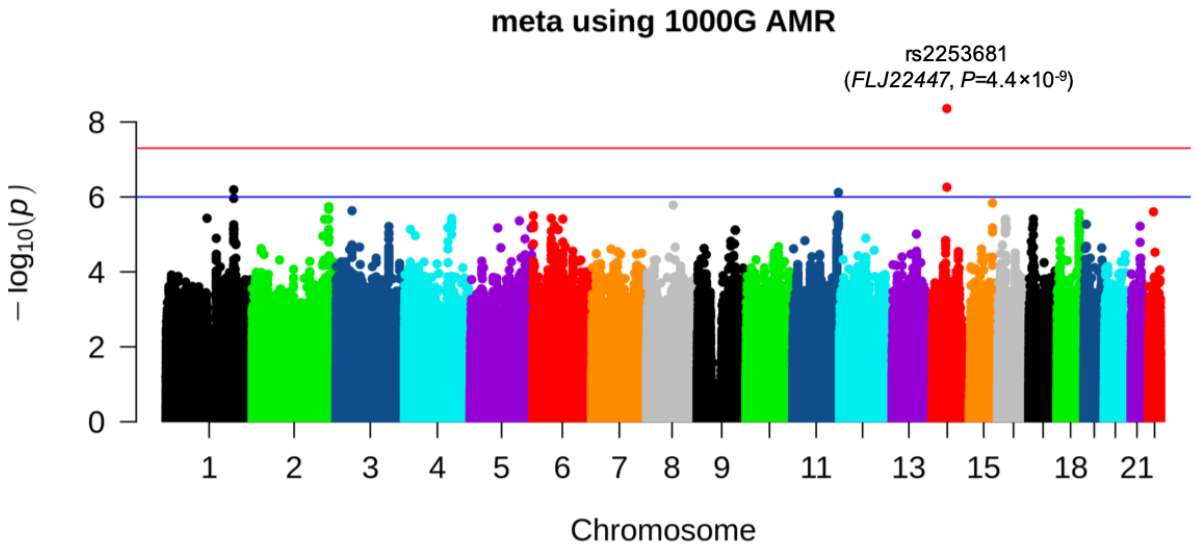


<u>Supplementary Figure S1</u> – The omics data distribution from the EVA-PR cohort
Expression and methylation in nasal airway epithelial cells



<u>Supplementary Figure S2</u> – Manhattan plot of meta-analysis results using 1000 Genome AMR as the imputation reference panel: Manhattan plot showing the summary meta-analysis results of HPR, GALA II, GACRS, and SCAALA. HPR, GALA II and GACRS were re-imputed using 1000 Genome AMR as the reference panel. SCAALA was not imputed.

Supplementary Table S1: Meta-analysis of GWAS of asthma exacerbation, for SNPs associated with asthma in two previous meta-analyses of multi-ancestry population and UK Biobank

SNP	CHR: BP	Alt	Ref	In Cited papers		HPR			GACRS			GALA II			SCAALA			Meta	Nearby genes
				OR*	P#	AAF	OR	*P*	AAF	OR	*P*	AAF	OR	*P*	AAF	OR	*P*	*P*	
Loci reported by Demenais, F. *et al*. *Nat Genet* 2018; 50: 42-53																			
rs7705042	5: 141 492 419	C	A	0.92	7.90E-09	0.31	1.18	0.22	0.33	0.98	0.89	0.31	1.02	0.79	NA	NA	NA	0.51	*NDFIP1,GNDPA1,SPRY4*
rs1233578	6: 28 712 247	G	A	1.09	5.90E-07	0.24	0.94	0.69	0.15	0.99	0.95	0.19	1.13	0.18	0.30	0.81	0.30	0.38	*GPX5,TRIM27*
rs2325291	6: 90 986 686	A	G	0.91	2.20E-12	0.24	0.96	0.78	0.25	1.09	0.53	0.26	1.06	0.41	NA	NA	NA	0.42	*BACH2,GJA10,MAP3K7*
rs167769	12: 57 503 775	T	C	1.08	3.90E-09	0.33	1.02	0.87	0.40	0.96	0.72	0.39	1.04	0.62	NA	NA	NA	0.75	*STAT6,NAB2,LRP1*
rs17637472	17: 47 461 433	A	G	1.08	6.60E-09	0.29	0.86	0.30	0.25	1.08	0.60	0.23	1.05	0.57	NA	NA	NA	0.83	*ZNF652,PHB*
rs2855812	6: 31 472 720	T	G	1.10	8.90E-12	0.19	1.08	0.63	0.12	1.02	0.91	0.17	1	1.00	0.18	0.83	0.48	0.81	*MICB,HCP5,MCCD1*
rs2589561	10: 9 046 645	A	G	1.10	3.50E-09	0.13	1.02	0.92	0.11	1.14	0.52	0.12	1.13	0.26	0.18	1.17	0.48	0.23	*GATA3,CELF2*
rs12543811	8: 81 278 885	G	A	1.09	1.10E-10	0.42	1.01	0.96	0.45	1.05	0.68	0.47	1.13	0.07	NA	NA	NA	0.10	*TPD52,ZBTB10*
rs17806299	16: 11 199 980	A	G	0.91	2.70E-10	0.16	0.74	0.09	0.16	0.98	0.91	0.12	1.03	0.79	0.08	0.95	0.87	0.57	*CLEC16A,DEXI,SOCS1*
rs1420101	2: 102 957 716	T	C	1.12	3.90E-21	0.33	1.15	0.31	0.31	1.17	0.24	0.30	1.04	0.57	0.35	1.27	0.24	0.17	*IL1RL1,IL1RL2,IL18R1*
rs10455025	5: 110 404 999	C	A	1.15	9.40E-26	0.28	0.98	0.90	0.32	1.09	0.51	0.26	1.06	0.46	0.18	1.29	0.30	0.40	*SLC25A46,TSLP*
rs20541	5: 131 995 964	A	G	1.12	5.00E-16	0.23	0.92	0.58	0.31	0.85	0.23	0.36	1	0.98	0.20	1.24	0.33	0.47	*IL13,RAD50,IL4*
rs9272346	6: 32 604 372	G	A	0.86	5.70E-24	0.39	1.02	0.89	0.37	0.94	0.62	0.33	0.91	0.19	NA	NA	NA	0.23	*HLA-DRB1,HLA-DQA1*
rs992969	9: 6 209 697	A	G	0.86	7.20E-20	0.28	1.00	0.99	0.22	1.12	0.44	0.24	0.99	0.92	0.31	0.84	0.40	0.81	*RANBP6,IL33*
rs7927894	11: 76 301 316	T	C	1.10	2.20E-14	0.37	0.79	0.08	0.30	1.30	0.06	0.29	1	0.96	NA	NA	NA	0.99	*EMSY,LRRC32*
rs11071558	15: 61 069 421	G	A	0.89	1.30E-09	0.23	1.07	0.64	NA	NA	NA	0.18	1.06	0.51	NA	NA	NA	0.42	*RORA,NARG2,VPS13C*
rs2033784	15: 67 449 660	G	A	1.10	7.40E-15	0.37	0.98	0.87	0.39	0.58	1.19E-5	0.37	1	0.97	0.39	0.99	0.96	0.05	*SMAD3,SMAD6,AAGAB*
rs2952156	17: 37 876 835	A	G	1.15	2.20E-30	0.45	1.23	0.09	0.52	1.02	0.85	0.44	1.02	0.78	0.42	1.28	0.17	0.32	*ERBB2,PGAP3,MIEN1*
Loci reported by Zhu, Z. *et al*. *Nat Genet* 2018; 50: 857-864																			
rs7936070	11: 76 293 527	T	G	1.08	2.81E-28	0.47	0.92	0.53	0.42	1.23	0.09	0.45	1	0.98	NA	NA	NA	0.64	*C11orf30,LOC100506127,PRKRIR*
rs72823641	2: 102 936 159	A	T	0.89	1.58E-27	0.11	0.79	0.27	0.08	0.94	0.77	0.08	1.1	0.45	NA	NA	NA	0.98	*IL1R1,IL1RL1,IL1RL2,IL18R1,IL18RAP,MIR4772,SLC9A2, SLC9A4*
rs56062135	15: 67 455 630	T	C	1.16	1.56E-22	0.18	1.20	0.26	0.18	0.61	0.0005	0.15	1.21	0.04	0.11	1.16	0.62	0.58	*SMAD3*
rs36045143	16: 11 224 966	G	A	0.93	1.83E-21	0.20	0.82	0.20	0.18	0.93	0.62	0.16	0.96	0.67				0.27	*CLEC16A,DEXI*
rs1837253	5: 110 401 872	T	C	0.93	4.38E-21	0.23	0.90	0.50	0.23	0.99	0.96	0.27	0.89	0.14	0.24	0.90	0.62	0.13	*TSLP*
rs7705653	5: 110 142 816	G	A	1.14	1.12E-19	0.26	0.83	0.19	0.21	1.16	0.34	0.25	0.92	0.33	NA	NA	NA	0.34	*SLC25A46,TMEM232*
rs28393318	4: 38 784 267	G	A	0.92	2.14E-19	0.39	0.88	0.32	0.25	1.00	0.98	0.28	1	0.95	NA	NA	NA	0.69	*FAM114A1,MIR574,TLR1,TLR6,TLR10*
rs869402	17: 38 068 043	T	C	0.89	4.15E-17	0.29	0.66	0.003	0.34	1.01	0.96	0.31	0.96	0.59	NA	NA	NA	0.11	*ERBB2,GRB7,GSDMA,GSDMB,IKZF3,LRRC3C,MIEN1, MIR4728,ORMDL3,PGAP3,PNMT,STARD3,TCAP,ZPBP2*
rs34290285	2: 242 698 640	A	G	0.93	5.17E-17	0.26	1.16	0.33	NA	NA	NA	0.21	0.92	0.30	NA	NA	NA	0.66	*D2HGDH,GAL3ST2*
rs10174949	2: 8 442 248	A	G	0.94	1.70E-16	0.24	1.11	0.46	0.23	0.89	0.41	0.26	0.93	0.37	NA	NA	NA	0.44	*LINC00299*
rs9911533	17: 3 877 5476	C	T	0.92	9.70E-16	0.33	1.09	0.55	0.35	1.11	0.42	0.31	0.95	0.52	NA	NA	NA	0.94	*KRT24,KRT222,SMARCE1*
rs12413578	10: 9 049 253	T	C	0.91	1.09E-14	0.10	0.72	0.15	0.10	0.99	0.96	0.07	1.02	0.88	NA	NA	NA	0.58	*HV745896*
rs6881270	5: 35 879 095	T	C	0.91	1.53E-14	0.18	0.97	0.87	0.17	0.93	0.63	0.18	1.05	0.58	NA	NA	NA	0.85	*CAPSL,IL7R,LOC100506406,SPEF2,UGT3A1*
rs10876864	12: 56 401 085	G	A	1.05	1.41E-13	0.50	0.96	0.73	0.33	1.25	0.09	0.37	1.07	0.37	0.60	0.95	0.77	0.20	*CDK2,ERBB3,IKZF4,PA2G4,RAB5B,RPL41,RPS26,SUOX, ZC3H10*
rs1059513	12: 57 489 709	C	T	0.92	7.65E-13	0.11	0.98	0.93	0.08	1.06	0.79	0.09	1.16	0.23	0.10	0.72	0.27	0.30	*GPR182,MYO1A,NAB2,RDH16,SDR9C7,STAT6,TAC3, TMEM194A,ZBTB39*
rs56267605	4: 123 363 109	C	A	1.05	2.56E-12	0.30	1.02	0.90	0.44	0.89	0.33	0.37	0.94	0.42	NA	NA	NA	0.31	*ADAD1,IL2,IL21,IL21-AS1,KIAA1109*
rs61839660	10: 6 094 697	T	C	1.12	2.30E-11	0.05	1.13	0.67	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.67	*IL2RA,RBM17*
rs2706362	5: 131 925 187	C	T	1.06	3.75E-11	0.32	0.95	0.73	0.19	1.19	0.27	0.26	1.04	0.60	NA	NA	NA	0.49	*IL13,RAD50*
rs1214598	1: 167 426 424	A	G	0.95	5.14E-11	0.28	1.26	0.10	0.27	1.06	0.65	0.25	1.05	0.52	NA	NA	NA	0.16	*CD247*
rs659529	11: 11 143 6896	T	A	0.95	6.03E-11	0.42	1.13	0.36	0.27	1.12	0.40	0.31	1.06	0.43	NA	NA	NA	0.17	*ALG9,BTG4,C11orf1,C11orf88,FDXACB1,LAYN,MIR34B, MIR34C,PPP2R1B,SIK2*
rs2766664	20: 52 171 241	A	G	1.08	8.07E-11	0.20	0.94	0.68	0.23	1.03	0.85	0.22	0.83	0.02	0.26	0.92	0.71	0.05	*LOC101927770,ZNF217*
rs2169282	9: 6 350 235	A	G	1.09	1.80E-10	0.49	0.97	0.80	0.40	1.13	0.34	0.41	1	0.97	NA	NA	NA	0.80	*GLDC,UHRF2*
rs10414065	19: 33 721 455	T	C	0.91	2.63E-10	0.05	0.96	0.90	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.90	*SLC7A10*
rs6461503	7: 20 560 996	C	T	0.95	3.19E-10	0.49	0.99	0.93	0.37	0.91	0.45	0.44	1.02	0.80	0.61	0.77	0.14	0.89	*ITGB8*

Ref: reference allele; Alt: alternative allele; AAF: alternative allele frequency; OR: odds ratio. Human Genome version: hg19.

*: This column is odds ratio from multi-ancestry meta-analysis in Demenais, F. *et al*. *Nat Genet* 2018; 50: 42-53 and from asthma/allergy meta-analysis in Zhu, Z. *et al*. *Nat Genet* 2018; 50: 857-864.

#: This column is *P*-value from multi-ancestry meta-analysis in Demenais, F. *et al*. *Nat Genet* 2018; 50: 42-53 and from asthma/allergy meta-analysis in Zhu, Z. *et al*. *Nat Genet* 2018; 50: 857-864.

<u>Supplementary Table S2</u>: Analysis of association between previously published SNPs for asthma exacerbations or hospitalizations and severe asthma exacerbations in the current meta-analysis of GWAS

SNP	CHR: BP	Gene	Alt	Ref	HPR			GACRS			GALA II			SCAALA			Meta	Ref
					AAF	OR	*P*	AAF	OR	*P*	AAF	OR	*P*	AAF	OR	*P*	*P*	
rs1800925	5: 131 992 809	*IL13*	T	C	0.28	0.86	0.31	0.20	0.98	0.88	0.28	1.03	0.71	NA	NA	NA	*0.86*	*1*
rs1805011	16: 27 373 872	*IL4RA*	C	A	0.24	1.00	1.00	0.15	0.81	0.22	0.20	1.01	0.89	NA	NA	NA	*0.73*	*2*
rs1801275	16: 27 374 400	*IL4RA*	G	A	0.37	0.91	0.50	0.29	0.91	0.46	0.35	1.05	0.50	0.51	1.02	0.92	*0.99*	*2*
rs4950928	1: 203 155 882	*CHI3L1*	G	C	0.18	0.73	0.08	0.17	0.92	0.60	0.17	1.09	0.35	NA	NA	NA	*0.09*	*3*
rs7216389	17: 38 069 949	*ORMDL3*	C	T	0.30	0.63	1.6E-3	0.34	0.99	0.97	0.31	1.04	0.59	0.28	0.84	0.38	*0.06*	*4*
rs6967330	7: 105 658 451	*CDHR3*	A	G	0.26	1.20	0.21	0.16	1.13	0.49	0.23	1.06	0.49	0.26	0.98	0.92	*0.20*	*5*
rs1099729	12: 97 251 586	*CTNNA3*	C	T	0.06	1.11	0.69	NA	NA	NA	0.06	1.16	0.30	NA	NA	NA	*0.46*	*6*
rs9587342	13: 107 936 790	*FAM155A*	A	G	0.41	0.93	0.59	0.47	0.97	0.82	0.45	0.99	0.84	0.40	1.33	0.13	*0.95*	*7**
rs6426881	1: 164 816 726	*PBX1*	T	C	0.11	1.20	0.36	0.12	0.99	0.96	0.13	0.94	0.55	0.09	1.06	0.86	*0.92*	*7*
rs1074119	7: 3 196 333	*CARD11*	T	C	0.44	0.99	0.92	0.41	1.07	0.58	0.44	0.95	0.48	NA	NA	NA	*0.44*	*7*
rs858928	2: 50 892 009	*NRXN1*	A	C	0.18	0.96	0.80	0.15	1.28	0.18	0.18	1.03	0.77	NA	NA	NA	*0.51*	*7*
rs12201938	6: 7 026 562	*RREB1*	A	G	0.09	0.82	0.40	0.08	0.64	0.03	0.08	1.09	0.52	0.05	1.09	0.83	*0.52*	*7*
rs9325122	5:148 202 936	*ADRβ2*	C	T	0.28	0.98	0.92	0.23	1.07	0.66	0.22	0.92	0.32	NA	NA	NA	*0.51*	*8*
rs1432622	5:148203762	*ADRβ2*	T	C	0.37	1.09	0.53	0.26	1.09	0.54	0.30	0.92	0.26	NA	NA	NA	*0.70*	*8*
rs1432623	5:148204008	*ADRβ2*	C	T	0.37	1.09	0.53	0.26	1.09	0.54	0.30	0.92	0.26	NA	NA	NA	*0.70*	*8*
rs11168068	5:148204121	*ADRβ2*	C	T	0.37	1.09	0.53	0.26	1.09	0.54	0.30	0.92	0.26	NA	NA	NA	*0.70*	*8*
rs17778257	5:148204577	*ADRβ2*	T	A	0.37	1.18	0.20	0.42	1.05	0.70	0.37	1.03	0.66	NA	NA	NA	*0.29*	*8*
rs2400706	5:148204864	*ADRβ2*	T	C	0.26	0.72	0.03	0.31	0.88	0.32	0.32	1.04	0.55	NA	NA	NA	*0.43*	*8*
rs2895795	5:148204966	*ADRβ2*	A	T	0.26	0.72	0.03	0.31	0.88	0.32	0.33	1.05	0.54	NA	NA	NA	*0.45*	*8*
rs2400707	5:148205052	*ADRβ2*	A	G	0.37	1.10	0.49	0.26	1.09	0.54	0.29	0.92	0.27	NA	NA	NA	*0.73*	*8*
rs2053044	5:148205372	*ADRβ2*	A	G	0.37	1.10	0.49	0.26	1.09	0.52	0.29	0.92	0.25	NA	NA	NA	*0.71*	*8*
rs12654778	5:148205741	*ADRβ2*	A	G	0.37	1.18	0.20	0.42	1.04	0.72	0.37	1.02	0.74	0.31	0.65	0.02	*0.75*	*8*
rs11168070	5:148205927	*ADRβ2*	G	C	0.28	0.98	0.89	0.23	1.06	0.70	0.22	0.92	0.30	NA	NA	NA	*0.47*	*8*
rs11959427	5:148206028	*ADRβ2*	C	T	0.29	0.97	0.86	0.23	1.06	0.70	0.22	0.92	0.30	NA	NA	NA	*0.46*	*8*
rs1801704	5:148206375	*ADRβ2*	C	T	0.29	0.98	0.90	0.23	1.04	0.78	0.22	0.92	0.27	0.23	1.17	0.45	*0.56*	*8*
rs1042713	5:148206440	*ADRβ2*	A	G	0.45	1.29	0.05	0.46	1.07	0.58	0.44	1.01	0.92	0.46	0.89	0.52	*0.36*	*8*
rs1042714	5:148206473	*ADRβ2*	G	C	0.29	0.97	0.86	0.23	1.04	0.78	0.22	0.92	0.27	0.23	1.16	0.48	*0.53*	*8*
rs1042717	5:148206646	*ADRβ2*	A	G	0.26	0.70	0.02	0.31	0.90	0.39	0.33	1.06	0.43	0.31	0.97	0.89	*0.54*	*8*
rs1042718	5:148206917	*ADRβ2*	A	C	0.24	0.67	0.01	0.28	0.88	0.36	0.31	1.12	0.13	0.29	1.01	0.97	*0.91*	*8*
rs1042720	5:148207633	*ADRβ2*	A	G	0.43	0.79	0.06	NA	NA	NA	0.46	1.00	0.98	0.46	1.25	0.22	*0.69*	*8*

Ref: reference allele; Alt: alternative allele; AAF: alternative allele frequency; OR: odds ratio. Human Genome version: hg19.

* Top 5 out of 160 SNPs used in asthma exacerbations prediction in 7 are shown.

1. *Hunninghake GM, Soto-Quiros ME, Avila L, Su J, Murphy A, Demeo DL, et al. Polymorphisms in IL13, total IgE, eosinophilia, and asthma exacerbations in childhood. J Allergy Clin Immunol 2007; 120:84-90.*
2. *Wenzel SE, Balzar S, Ampleford E, Hawkins GA, Busse WW, Calhoun WJ, et al. IL4R alpha mutations are associated with asthma exacerbations and mast cell/IgE expression. Am J Respir Crit Care Med 2007; 175:570-6.*
3. *Cunningham J, Basu K, Tavendale R, Palmer CN, Smith H, Mukhopadhyay S. The CHI3L1 rs4950928 polymorphism is associated with asthma-related hospital admissions in children and young adults. Ann Allergy Asthma Immunol 2011; 106:381-6.*
4. *Bisgaard H, Bonnelykke K, Sleiman PM, Brasholt M, Chawes B, Kreiner-Moller E, et al. Chromosome 17q21 gene variants are associated with asthma and exacerbations but not atopy in early childhood. Am J Respir Crit Care Med 2009; 179:179-85.*
5. *Bonnelykke K, Sleiman P, Nielsen K, Kreiner-Moller E, Mercader JM, Belgrave D, et al. A genome-wide association study identifies CDHR3 as a susceptibility locus for early childhood asthma with severe exacerbations. Nat Genet 2014; 46:51-5.*
6. *McGeachie MJ, Wu AC, Tse SM, Clemmer GL, Sordillo J, Himes BE, et al. CTNNA3 and SEMA3D: Promising loci for asthma exacerbation identified through multiple genome-wide association studies. J Allergy Clin Immunol 2015; 136:1503-10.*
7. *Xu M, Tantisira KG, Wu A, Litonjua AA, Chu JH, Himes BE, et al. Genome Wide Association Study to predict severe asthma exacerbations in children using random forests classifiers. BMC Med Genet 2011; 12:90.*
8. *Hawkins GA, Tantisira K, Meyers DA, Ampleford EJ, Moore WC, Klanderman B, et al. Sequence, Haplotype, and Association Analysis of ADRβ2 in a Multiethnic Asthma Case-Control Study. Am J Respir Crit Care Med 2006; 174:1101–9.*

<u>Supplementary Table S3</u>: Top 20 eQTLs for rs2253681 in EVA-PR nasal epithelial cells and replication results from PIAMA

Gene	Chr	Start	End	EVA-PR			PIAMA		Meta-analysis	
				Effect	*P*-value	*FDR*[*]	Effect	*P*-value	Effect	*P*-value
SRF	6	43 139 032	43 149 244	-0.0723	5.84×10^{-4}	1.00	-0.0921	8.26×10^{-3}	-0.0776	1.64×10^{-5}
OR2A20P	7	143 947 766	143 948 696	-0.1858	6.27×10^{-4}	1.00	NA	NA	NA	NA
RASIP1	19	49 223 841	49 243 970	-0.1083	9.93×10^{-4}	1.00	-0.1064	1.40×10^{-1}	-0.1080	3.08×10^{-4}
LOC100128398	19	58 514 261	58 518 574	-0.0845	1.56×10^{-3}	1.00	NA	NA	NA	NA
SNORA53	12	98 993 412	98 993 662	0.2324	1.56×10^{-3}	1.00	NA	NA	NA	NA
HPGDS	4	95 219 706	95 264 027	0.1359	2.14×10^{-3}	1.00	0.0868	7.27×10^{-1}	0.1344	2.05×10^{-3}
NPTXR	22	39 214 455	39 240 017	-0.0864	2.41×10^{-3}	1.00	-0.1737	5.39×10^{-2}	-0.0943	5.13×10^{-4}
ASCC1	10	73 855 789	73 975 867	0.0352	2.42×10^{-3}	1.00	0.0562	1.44×10^{-1}	0.0369	8.83×10^{-4}
SOX4	6	21 593 971	21 598 849	-0.0840	2.59×10^{-3}	1.00	-0.0367	3.78×10^{-1}	-0.0694	2.76×10^{-3}
ZNF675	19	23 835 707	23 870 017	0.0674	2.82×10^{-3}	1.00	-0.0524	4.63×10^{-1}	0.0565	8.62×10^{-3}
PPIP5K1	15	43 825 659	43 877 090	-0.0356	2.85×10^{-3}	1.00	0.0207	4.89×10^{-1}	-0.0279	1.19×10^{-2}
TCF7L2	10	114 710 008	114 927 436	-0.0598	3.05×10^{-3}	1.00	-0.0266	4.01×10^{-1}	-0.0502	3.19×10^{-3}
SSR4P1	21	46 490 869	46 493 126	0.0693	3.27×10^{-3}	1.00	0.0078	9.56×10^{-1}	0.0676	3.63×10^{-3}
SNORD17	20	17 943 352	17 943 589	0.1407	3.34×10^{-3}	1.00	NA	NA	NA	NA
LOC100130691	2	178 148 235	178 257 419	0.0726	3.41×10^{-3}	1.00	NA	NA	NA	NA
TNNI3	19	55 663 135	55 669 100	-0.1318	3.49×10^{-3}	1.00	NA	NA	NA	NA
ARHGEF5	7	144 052 488	144 077 725	-0.0946	3.61×10^{-3}	1.00	-0.0399	3.49×10^{-1}	-0.0745	3.94×10^{-3}
LOC100132077	9	97 094 757	97 123 230	0.1005	4.04×10^{-3}	1.00	NA	NA	NA	NA
HACE1	6	105 175 967	105 307 794	0.0405	4.08×10^{-3}	1.00	0.0634	1.92×10^{-1}	0.0423	1.79×10^{-3}
NDUFS6	5	1 801 495	1 816 167	-0.0441	4.12×10^{-3}	1.00	0.0262	5.71×10^{-1}	-0.0371	1.09×10^{-2}

[*] *FDR* is adjusted for the whole genome in EVA-PR

Supplementary Table S4: Nominally significant pathways associated with severe asthma exacerbations with genes in the *FLJ22447* locus

Gene*	Pathway	*P*-value
PRKCH	REACTOME_SIGNALING_BY_GPCR	0.0084
PRKCH	REACTOME_PLATELET_ACTIVATION_SIGNALING_AND_AGGREGATION	0.0168
PRKCH	REACTOME_GPCR_DOWNSTREAM_SIGNALING	0.0315
PRKCH	GO_REGULATION_OF_IMMUNE_SYSTEM_PROCESS	0.0004
PRKCH	GO_REGULATION_OF_EPITHELIAL_CELL_DIFFERENTIATION	0.0024
PRKCH	GO_REGULATION_OF_CELL_PROLIFERATION	0.0035
PRKCH	GO_POSITIVE_REGULATION_OF_CELL_PROLIFERATION	0.0055
PRKCH	GO_PROTEIN_PHOSPHORYLATION	0.0153
PRKCH	GO_ENZYME_BINDING	0.0158
PRKCH	GO_POSITIVE_REGULATION_OF_GLIOGENESIS	0.0193
PRKCH	GO_REGULATION_OF_MULTICELLULAR_ORGANISMAL_DEVELOPMENT	0.0205
PRKCH	GO_POSITIVE_REGULATION_OF_EPITHELIAL_CELL_DIFFERENTIATION	0.0209
PRKCH	GO_PLATELET_ACTIVATION	0.0255
PRKCH	GO_POSITIVE_REGULATION_OF_DEVELOPMENTAL_PROCESS	0.0303
PRKCH	GO_POSITIVE_REGULATION_OF_CELL_DIFFERENTIATION	0.0340
PRKCH	GO_POSITIVE_REGULATION_OF_EPIDERMAL_CELL_DIFFERENTIATION	0.0384
PRKCH	GO_RAL_GTPASE_BINDING	0.0398
PRKCH	GO_REGULATION_OF_CELL_DIFFERENTIATION	0.0444
PRKCH	GO_TRANSFERASE_ACTIVITY_TRANSFERRING_PHOSPHORUS_CONTAINING_GROUPS	0.0448
PRKCH	GO_POSITIVE_REGULATION_OF_IMMUNE_SYSTEM_PROCESS	0.0460
PRKCH	GO_ADENYL_NUCLEOTIDE_BINDING	0.0483
SNAPC1	GO_NUCLEAR_TRANSCRIPTION_FACTOR_COMPLEX	0.0028
SNAPC2	GO_TRANSCRIPTION_FACTOR_COMPLEX	0.0295
HIF1A	KEGG_MTOR_SIGNALING_PATHWAY	0.0341
HIF1A	GO_REGULATION_OF_IMMUNE_SYSTEM_PROCESS	0.0004
HIF1A	GO_REGULATION_OF_HEMOPOIESIS	0.0005
HIF1A	GO_COLUMNAR_CUBOIDAL_EPITHELIAL_CELL_DEVELOPMENT	0.0011
HIF1A	GO_CELLULAR_COMPONENT_MORPHOGENESIS	0.0012
HIF1A	GO_CELLULAR_RESPONSE_TO_INTERLEUKIN_1	0.0016
HIF1A	GO_ESTABLISHMENT_OF_LOCALIZATION_BY_MOVEMENT_ALONG_MICROTUBULE	0.0020
HIF1A	GO_RESPONSE_TO_INTERLEUKIN_1	0.0028
HIF1A	GO_NUCLEAR_TRANSCRIPTION_FACTOR_COMPLEX	0.0028
HIF1A	GO_CELL_DEVELOPMENT	0.0029
HIF1A	GO_REGULATION_OF_CELL_PROLIFERATION	0.0035
HIF1A	GO_REGULATION_OF_MYELOID_CELL_DIFFERENTIATION	0.0045
HIF1A	GO_ORGANELLE_TRANSPORT_ALONG_MICROTUBULE	0.0054
HIF1A	GO_POSITIVE_REGULATION_OF_CELL_PROLIFERATION	0.0055
HIF1A	GO_CYTOPLASMIC_REGION	0.0055
HIF1A	GO_EPITHELIAL_CELL_DEVELOPMENT	0.0068
HIF1A	GO_CYTOSKELETON_DEPENDENT_INTRACELLULAR_TRANSPORT	0.0079
HIF1A	GO_EMBRYONIC_HEART_TUBE_MORPHOGENESIS	0.0085
HIF1A	GO_CELL_PROJECTION_CYTOPLASM	0.0104
HIF1A	GO_HEART_MORPHOGENESIS	0.0108
HIF1A	GO_UBIQUITIN_LIKE_PROTEIN_LIGASE_BINDING	0.0117
HIF1A	GO_MORPHOGENESIS_OF_AN_EPITHELIUM	0.0127
HIF1A	GO_POSITIVE_REGULATION_OF_HEMOPOIESIS	0.0128
HIF1A	GO_ACUTE_INFLAMMATORY_RESPONSE	0.0138
HIF1A	GO_RECEPTOR_BINDING	0.0145
HIF1A	GO_RNA_POLYMERASE_II_TRANSCRIPTION_FACTOR_COMPLEX	0.0148
HIF1A	GO_REGULATION_OF_VASCULAR_ENDOTHELIAL_GROWTH_FACTOR_RECEPTOR_SIGNALING_PATHWAY	0.0154
HIF1A	GO_ENZYME_BINDING	0.0158
HIF1A	GO_TISSUE_MORPHOGENESIS	0.0160
HIF1A	GO_COLUMNAR_CUBOIDAL_EPITHELIAL_CELL_DIFFERENTIATION	0.0170
HIF1A	GO_REGULATION_OF_VASCULAR_ENDOTHELIAL_GROWTH_FACTOR_PRODUCTION	0.0177
HIF1A	GO_AXON_PART	0.0186
HIF1A	GO_DIGESTIVE_SYSTEM_DEVELOPMENT	0.0195
HIF1A	GO_REGULATION_OF_EPITHELIAL_CELL_PROLIFERATION	0.0196
HIF1A	GO_AXO_DENDRITIC_TRANSPORT	0.0201
HIF1A	GO_REGULATION_OF_MULTICELLULAR_ORGANISMAL_DEVELOPMENT	0.0205
HIF1A	GO_REGULATION_OF_TRANSCRIPTION_FROM_RNA_POLYMERASE_II_PROMOTER	0.0217
HIF1A	GO_POSITIVE_REGULATION_OF_NUCLEOTIDE_METABOLIC_PROCESS	0.0225

HIF1A	GO_NEGATIVE_REGULATION_OF_MULTICELLULAR_ORGANISMAL_PROCESS	0.0227
HIF1A	GO_CELL_MORPHOGENESIS_INVOLVED_IN_DIFFERENTIATION	0.0229
HIF1A	GO_HEART_DEVELOPMENT	0.0244
HIF1A	GO_TUBE_MORPHOGENESIS	0.0248
HIF1A	GO_POSITIVE_REGULATION_OF_NEUROBLAST_PROLIFERATION	0.0270
HIF1A	GO_EMBRYONIC_HEART_TUBE_DEVELOPMENT	0.0270
HIF1A	GO_CELLULAR_RESPONSE_TO_OXYGEN_LEVELS	0.0277
HIF1A	GO_TRANSCRIPTION_FACTOR_COMPLEX	0.0295
HIF1A	GO_POSITIVE_REGULATION_OF_DEVELOPMENTAL_PROCESS	0.0303
HIF1A	GO_CELLULAR_RESPONSE_TO_STRESS	0.0321
HIF1A	GO_POSITIVE_REGULATION_OF_CELL_DIFFERENTIATION	0.0340
HIF1A	GO_DOPAMINERGIC_NEURON_DIFFERENTIATION	0.0341
HIF1A	GO_STEM_CELL_DIFFERENTIATION	0.0381
HIF1A	GO_POSITIVE_REGULATION_OF_TRANSCRIPTION_FROM_RNA_POLYMERASE_II_PROMOTER	0.0391
HIF1A	GO_CELLULAR_RESPONSE_TO_CYTOKINE_STIMULUS	0.0399
HIF1A	GO_AXON	0.0416
HIF1A	GO_OUTFLOW_TRACT_MORPHOGENESIS	0.0424
HIF1A	GO_TISSUE_REMODELING	0.0432
HIF1A	GO_REGULATION_OF_CELL_DIFFERENTIATION	0.0444
HIF1A	GO_DEVELOPMENTAL_MATURATION	0.0447
HIF1A	GO_POSITIVE_REGULATION_OF_IMMUNE_SYSTEM_PROCESS	0.0460
HIF1A	GO_REGULATION_OF_SMOOTH_MUSCLE_CELL_PROLIFERATION	0.0467
HIF1A	GO_TRANSCRIPTION_FACTOR_ACTIVITY_RNA_POLYMERASE_II_TRANSCRIPTION_FACTOR_BINDING	0.0471
HIF1A	GO_RNA_POLYMERASE_II_TRANSCRIPTION_FACTOR_ACTIVITY_SEQUENCE_SPECIFIC_DNA_BINDING	0.0480

* The genes (*TMEM30B, PRKCH, LOC101927780, HIF1A-AS1, HIF1A-AS2, SNAPC1, FLJ22447* and *HIF1A*) in *FLJ22447* locus and also included in the nominally significant pathways.

Supplementary Table S5: Results for SNP rs2253681 (minor allele = A) and severe asthma exacerbations using different imputation reference panels

Reference panels	HPR (genotyped)			GACRS (imputed)			GALA II† (genotyped)			SCAALA* (genotyped)			Meta	
	MAF	OR	*P*	MAF	OR	*P*	MAF	OR	*P*	MAF	OR	*P*	OR	*P*
HRC	0.20	1.49	0.013	0.11	1.38	0.12	0.16	1.54	2.3E-5	0.24	1.92	3.2E-3	1.55	6.3E-9
1000G AMR	0.20	1.49	0.013	0.11	1.37	0.12	0.16	1.55	1.5E-5				1.55	4.4E-9

SNP rs2253681 was genotyped in HPR, GALA II and SCAALA, and only imputed in GACRS.

†Although rs2253681 was a genotyped SNP in GALA II, there was one sample with missing genotype. This sample had different imputed genotypes for rs2253681 between HRC and 1000G AMR, which caused the small discrepancy in p-values and ORs.

*SCAALA data were not imputed. Thus, SCAALA results were not affected by reference panels.