

Whole Genome Sequencing Identifies *CRISPLD2* as a Lung Function Gene in Children With Asthma

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e-Appendix 1.

Supplemental Methods

Asthma ascertainment criteria in CRA

The methacholine challenge test was performed on a separate visit in children with an FEV₁ of at least 65% of predicted¹. The inhalation protocol consisted of five breaths of saline solution followed by one breath of a 1 mg/mL methacholine solution, one and four breaths of a 5 mg/mL methacholine solution, and one breath of a 25 mg/mL methacholine solution provided with a DeVilbiss 646 nebulizer (Sunrise Medical; Carlsbad, CA, US). Bronchial responsiveness was calculated as the provocative dose of methacholine resulting in a 20% drop in FEV₁ from baseline (PD₂₀). A strict definition of asthma affection status was defined requiring the presence of methacholine dose responsiveness ($\leq 8.58 \mu\text{M}$). At enrollment, a blood sample was drawn from the participating children and both their parents (i.e. trios) and the children's lung function was investigated by means of spirometry before and after administration of a bronchodilator.

Baseline Lung Function

Baseline lung function was measured by spirometry using a Survey Tach Spirometer (Warren E. Collins; Braintree, MA, US) with the children seated and wearing a nose clip. Prior to assessment, the children were told to withhold short-acting bronchodilators for at least 4 hours. The best forced expiratory volume in the 1st second (FEV₁) and corresponding forced vital capacity (FVC) values from 3-5 acceptable flow-volume curves were selected for analysis of FEV₁ and FEV₁/FVC ratio according to the American Thoracic Society guidelines². The measurements were calibrated for gender, age and height according to reference values for Mexican Americans³.

Bronchodilator Response

After completing baseline spirometry, the children were given 200 μg (2 puffs) of an albuterol pressurized metered-dose inhaler (pMDI) using a spacer device. Spirometry was repeated after 15 min, capturing post-bronchodilator FEV₁ and FEV₁/FVC ratio as described above.

Replication Study Populations

We identified six validation cohorts including children with ascertained asthma diagnosis primarily from the NHLBI Trans-Omics for Precision Medicine (TOPMed) consortium (CAMP⁴: Childhood Asthma Management Program, HPR: Hartford-Puerto Rico⁵, GALAI⁶: Gene-Environments and Admixture in Latino Americans, SAGE⁶: Study of African Americans, Asthma, Genes and the Environment, SAPPHIRE⁷: Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity) and the Copenhagen Prospective Study on Asthma in Childhood^{8,9} (COPSAC) cohort. Among these, three cohorts utilized similar criteria for asthma

classification as GACRS; namely AHR (CAMP₄, Hartford-PR₅, COPSAC₈: case-status was strongly associated with AHR) and three did not include AHR in their classification (GALAI₆, SAGE₆, SAPPHIRE₇). We provide a brief summary of each cohort here.

Replication cohorts ascertained utilizing asthma diagnosis with confirmed AHR

HPR (Hartford-Puerto Rico)

Brief Cohort description: The details of subject recruitment and study methods have been published previously^{10,11}. In brief, from September 2003 to July 2008, 449 Puerto Rican children of age 6-14 years were recruited from elementary/middle schools in Hartford, Connecticut; and from March 2009 to June 2010, 678 Puerto Rican children living in San Juan, Puerto Rico, were recruited using a multistage probability sample design. 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 Connecticut Children's Medical Center (Hartford, CT), the University of Puerto Rico (San Juan, PR), Brigham and Women's Hospital (Boston, MA), and the University of Pittsburgh (Pittsburgh, PA).

Asthma ascertainment/diagnosis criteria: Asthma was defined as physician diagnosis and at least one episode of wheeze in the prior year; controls were defined as no physician diagnosis and no wheeze in the prior year. Spirometry was conducted according to American Thoracic Society criteria^{2,12}; spirometry was repeated 15 minutes after administration of 200 µg of albuterol via metered-dose inhaler. Bronchodilator response and airway responsiveness to methacholine was measured but was not the inclusion criteria. Of the 1,127 study participants, 943 had genome-wide genotypic data. Of these 943 children, 884 also had pre-bronchodilator measures of lung function, and 819 also had post-bronchodilator measures of lung function, Of those, 490 cases were included for the current analyses. Of the HPR cases who did undergo methacholine challenge testing, majority of them had airway hyperresponsiveness (AHR). All multivariable models of lung function were adjusted for age, sex, height, study site (Hartford vs. Puerto Rico) and principal components.

CAMP (Childhood Asthma Management Program)

Brief cohort description: CAMP is a multi-center randomized clinical trial that recruited children 5-12 years of age (n=1,041) with mild to moderate asthma and airway hyperresponsiveness (AHR) to determine the long-term (approximately 16.5 years of follow-up) effects of three inhaled treatments (placebo, nedocromil, or budesonide).

Asthma ascertainment/diagnosis criteria: Chronic asthma was determined by one or more of the following, for at least 6 months in the year prior to interview: asthma symptoms at least two times per week, at least two usages per week of an inhaled bronchodilator and daily asthma medication.

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Participants were also required to complete a screening period (28 days) providing evidence of mild to moderate asthma. Clinics determined airway responsiveness by the decrease in FEV1 after increasing concentrations of methacholine challenge using the Wright nebulizer–tidal breathing technique.

Replication cohorts ascertained utilizing a doctor’s diagnosis of asthma

GALA II (Gene-Environments and Admixture in Latino Americans)

Brief cohort description: The GALA II study includes 4,436 Latino asthma cases and controls recruited from community clinics and hospitals from New York, Chicago, San Francisco, Houston, and Puerto Rico (2,275 cases, 2,161 controls). Atopy was not an inclusion criteria for the study.

Asthma ascertainment/diagnosis criteria: Asthma was defined as having a history of physician-diagnosed asthma and two or more asthma symptoms (wheezing, coughing, and/or shortness of breath) in the preceding two years.

SAGE (Study of African Americans, Asthma, Genes and the Environment)

Brief cohort description: The SAGE study includes 1,989 African American asthma cases and controls recruited from clinics in the San Francisco Bay Area (1176 cases, 813 controls). Asthma was defined as having a history of physician-diagnosed asthma and two or more asthma symptoms (wheezing, coughing, and/or shortness of breath) in the preceding two years. Atopy was not an inclusion criteria for the study.

Asthma ascertainment/diagnosis criteria: Asthma was defined as having a history of physician-diagnosed asthma and two or more asthma symptoms (wheezing, coughing, and/or shortness of breath) in the preceding two years. Atopy was not an inclusion criteria for the study.

SAPPHIRE (Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity)

Brief cohort description: The SAPPHIRE cohort is an ongoing study to identify the genetic predictors of asthma controller medication response among a population-based sample of individuals with asthma. Specifically, the cohort includes members of a large health system, which serves southeast Michigan and the greater Detroit metropolitan area.

Asthma ascertainment/diagnosis criteria: There were a total of 802 asthmatics included in this analysis. Potential participants were identified from health care claims and recorded diagnoses. Eligibility criteria for SAPPHIRE participants were as follows: age 12 to 56 years, a physician’s diagnosis of asthma, and no prior diagnosis of chronic obstructive pulmonary disease or congestive heart failure. Individuals who consented to participate also had a detailed research evaluation, which included assessing lung function, completing a study survey, and measuring

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bronchodilator response. Of the 802 SAPPHERE individuals included in the current study, 585 had childhood onset (reported age of diagnosis <18 years); 216 had adult onset asthma (reported age of diagnosis \geq 18 years); and one individual was missing information on age of onset.

COPSAC2000 (Copenhagen Prospective Study on Asthma in Childhood)

Brief cohort description: High-risk prospective birth cohort of 411 children born during 1998-2001 to mothers with doctor-diagnosed asthma in greater Copenhagen, Denmark. The cohort was enrolled at age 1 month and attended the research clinic for clinical examinations at ages 1 and 6 month and half-yearly hereafter till age 7. Acute care visits were arranged upon onset of any respiratory symptoms and symptom burden between visits were captured in a day-to-day diary fulfilled from birth onwards.

Asthma ascertainment/diagnosis criteria: A 3-month trial of inhaled corticosteroids (ICS) was prescribed to children suffering: 1) at least 5 dairy-verified episodes of troublesome lung symptoms within 6 months, each lasting at least 3 consecutive, 2) 4 weeks of consecutive troublesome lung symptoms, or 3) acute severe symptoms requiring a course of oral corticosteroids and/or admission to a pediatric ED. Asthma was diagnosed solely by the COPSAC pediatricians in children responding to such 3-months ICS trial and relapsing after stopping treatment. Current asthma by age 6 was diagnosed in children fulfilling the above diagnostic criteria and still depending on ICS in their 6th year of life. Asthma diagnosis was strongly associated with AHR to metacholine measured from age 1 month and onwards⁹.

Sequencing and quality control

Briefly, we submitted samples to the University of Washington, Northwest Genome Center for 30x average coverage PCR-free WGS. Reads were aligned to GRCh37 at the Informatics Resource Center (IRC), and variants were jointly called using the GotCloud vt pipeline, using a support vector machine to filter variants; additional filters for Mendelian errors and heterozygosity were also applied. Subject level QC on data released by the IRC included coverage, duplication, DNA fingerprints concordance, sample homo and heterozygosity, and contamination.

We performed additional QC on samples and variants passing IRC. To identify subject outliers, we examined transition to transversion ratio, heterozygous to homozygous genotype ratio, proportion of variants in dbSNP, call rate, inbreeding coefficient, Mendelian errors and gender errors. Relatedness was confirmed using the software KING¹³ and population outliers were identified using TRACE. Genotypes with depth less

than 10 were excluded. Additional filtering on the variants was based on the concordance rate, mean depth, Mendelian errors, and call rate. INDELS and multiallelic variants were excluded in this analysis.

e-Table 1. The table shows all SNPs with association p-value below 10^{-5} for baseline FEV1/FVC (unadjusted) and the corresponding p-values for the adjusted trait.

rs ID	Chr	Basepair	A1	A2	MAF	NINFF	Z-score	unadjusted model p-value	adjusted model p-value
rs12624042	2	1722883	G	A	0.131	122	-4.547	5.45E-06	2.72E-07
rs697210	12	104092996	C	T	0.399	214	-4.703	2.56E-06	1.30E-05
rs6564961	16	82079091	G	A	0.351	200	-4.661	3.15E-06	6.28E-06
rs8061420	16	82082010	C	T	0.35	208	-4.605	4.12E-06	2.40E-05
rs2966245	16	82106299	G	A	0.357	214	-4.782	1.74E-06	3.95E-06
rs2911422	16	82109474	C	G	0.394	210	-4.771	1.83E-06	7.64E-06
rs12931881	16	84879286	A	G	0.338	204	-5.031	4.88E-07	2.30E-05
rs12051168	16	84879324	C	T	0.392	210	-5.511	3.56E-08	5.61E-06
rs12051468	16	84879464	G	A	0.375	209	-4.776	1.78E-06	3.90E-05
rs12932773	16	84879920	A	G	0.354	206	-4.414	1.00E-05	1.62E-04
rs12919905	16	84880424	A	T	0.359	202	-5.44	5.34E-08	4.49E-06
rs11649180	16	85430844	C	T	0.257	183	-5.044	4.56E-07	2.41E-07

*Adjusted for gender, age and height. MAF: Minor Allele Frequency, NINFF: Number of informative families

e-Table 2. The table shows all SNPs with association p-value below 10^{-5} for PB FEV1/FVC (unadjusted) and the corresponding p-values for the adjusted trait.

rs ID	Chr	Basepair	A1	A2	MAF	NINFF	Z-score	unadjusted model p-value	adjusted model p-value
rs34281851	7	41553437	T	C	0.055	63	4.434	9.24E-06	1.30E-05
rs1410832	9	32741593	C	T	0.226	168	-4.459	8.24E-06	5.70E-05
rs1410833	9	32741649	G	C	0.226	168	-4.459	8.24E-06	5.70E-05
rs4888884	16	78979488	T	G	0.385	212	4.65	3.31E-06	6.20E-05
rs2966245	16	82106299	G	A	0.357	213	-4.438	9.10E-06	1.50E-05
rs11649180	16	85430844	C	T	0.257	183	-4.448	8.66E-06	9.17E-06
rs8079846	17	21367904	C	T	0.474	219	4.442	8.92E-06	1.60E-05
rs2203841	17	21378625	A	G	0.458	218	4.546	5.46E-06	1.30E-05

*Adjusted for gender, age and height. MAF: Minor Allele Frequency, NINFF: Number of informative families

e-Table 3. The table shows all SNPs with association p-value below 10^{-5} for baseline FEV1 (unadjusted) and the corresponding p-values for the adjusted trait.

rs ID	Chr	Basepair	A1	A2	MAF	NINFF	Z-score	unadjusted model p-value	adjusted model p-value
rs72775502	1	245316755	A	C	0.379	197	-4.775	1.80E-06	7.29E-01
rs9628692	1	245720262	A	C	0.362	209	4.601	4.21E-06	1.07E-01
rs77896577	1	245744896	A	G	0.157	141	4.496	6.94E-06	5.37E-02
rs4393798	2	43370728	A	G	0.082	81	-4.408	1.00E-05	6.29E-02
rs1978647	2	43371360	C	G	0.078	77	-4.559	5.13E-06	7.93E-02
rs138044470	3	112165660	C	A	0.03	40	4.524	6.06E-06	2.55E-01
rs6439251	3	130333768	G	A	0.458	215	4.519	6.21E-06	1.17E-01
rs7740935	6	163559154	A	T	0.143	125	-4.588	4.47E-06	6.39E-02
rs1033578	6	163559644	C	T	0.138	125	-4.475	7.65E-06	6.68E-02
rs1033579	6	163559907	C	T	0.138	125	-4.475	7.65E-06	6.68E-02
rs6908473	6	163560002	A	T	0.138	125	-4.475	7.65E-06	6.68E-02
rs6924563	6	163560038	T	C	0.137	124	-4.773	1.81E-06	4.97E-02
rs58304775	6	163560095	A	G	0.139	126	-4.415	1.00E-05	6.88E-02
rs57010913	6	163560097	G	A	0.139	126	-4.415	1.00E-05	6.88E-02
rs57444816	6	163560158	A	G	0.139	126	-4.415	1.00E-05	6.88E-02
rs6909176	6	163582608	T	C	0.119	111	-4.523	6.09E-06	2.59E-02
rs12539002	7	52577868	A	G	0.413	214	4.642	3.44E-06	6.02E-03
rs10081348	7	156375728	T	C	0.049	56	4.471	7.79E-06	5.32E-01
rs62517707	8	131408202	A	G	0.238	178	4.492	7.07E-06	7.04E-02
rs2102861	8	134519616	C	A	0.438	213	4.427	9.54E-06	1.49E-01
rs9644992	9	90027030	A	G	0.066	73	4.673	2.96E-06	5.69E-02
rs72761264	9	133072737	A	G	0.132	109	-4.524	6.06E-06	2.85E-03
rs11201438	10	86942568	A	G	0.257	177	4.58	4.65E-06	2.65E-02
rs1339907	10	86950656	T	C	0.262	179	4.704	2.56E-06	1.27E-02
rs1339908	10	86950658	T	C	0.262	179	4.704	2.56E-06	1.27E-02
rs17370747	10	86954878	G	A	0.239	177	4.523	6.10E-06	6.81E-03
rs11201447	10	86955624	T	C	0.295	193	4.415	1.00E-05	5.74E-02
rs2050795	10	86957751	C	T	0.295	193	4.415	1.00E-05	5.74E-02
rs7094082	10	86958017	A	G	0.265	186	4.414	1.00E-05	7.33E-02
rs1339914	10	86960054	A	T	0.268	185	4.461	8.17E-06	5.96E-02
rs1339915	10	86960078	T	C	0.268	185	4.461	8.17E-06	5.96E-02
rs12766774	10	86960524	G	A	0.268	185	4.461	8.17E-06	5.96E-02
rs12766218	10	86960634	T	C	0.268	185	4.461	8.17E-06	5.96E-02
rs11201452	10	86961299	A	T	0.268	185	4.461	8.17E-06	5.96E-02
rs12768920	10	86962827	G	A	0.268	185	4.461	8.17E-06	5.96E-02
rs11201453	10	86963611	C	T	0.268	185	4.461	8.17E-06	5.96E-02
rs1416924	10	86964119	C	T	0.268	185	4.461	8.17E-06	5.96E-02
rs12777141	10	86964444	G	A	0.268	185	4.461	8.17E-06	5.96E-02
rs12782135	10	86964500	G	A	0.319	204	4.423	9.73E-06	4.70E-02
rs11201454	10	86964566	C	A	0.268	185	4.461	8.17E-06	5.96E-02
rs11201455	10	86964789	T	C	0.268	185	4.461	8.17E-06	5.96E-02
rs1416925	10	86964927	C	T	0.268	185	4.461	8.17E-06	5.96E-02
rs1416926	10	86965064	A	T	0.268	185	4.461	8.17E-06	5.96E-02
rs1416927	10	86965204	G	A	0.268	185	4.461	8.17E-06	5.96E-02
rs1416929	10	86965265	A	G	0.268	185	4.461	8.17E-06	5.96E-02
rs11201456	10	86965535	G	A	0.268	185	4.461	8.17E-06	5.96E-02
rs11201457	10	86965572	G	C	0.268	185	4.461	8.17E-06	5.96E-02



rs11201459	10	86966069	C	T	0.26	179	4.599	4.25E-06	3.54E-02
rs11201461	10	86966202	G	A	0.26	179	4.599	4.25E-06	3.54E-02
rs11201462	10	86966316	C	A	0.26	179	4.599	4.25E-06	3.54E-02
rs11201463	10	86966361	G	T	0.26	179	4.599	4.25E-06	3.54E-02
rs11201464	10	86966369	A	G	0.26	179	4.599	4.25E-06	3.54E-02
rs11201465	10	86966491	C	T	0.26	179	4.599	4.25E-06	3.54E-02
rs11201466	10	86966577	T	A	0.26	179	4.599	4.25E-06	3.54E-02
rs11201467	10	86966590	G	A	0.26	179	4.599	4.25E-06	3.54E-02
rs11201468	10	86966732	T	C	0.26	179	4.599	4.25E-06	3.54E-02
rs11201469	10	86966777	T	C	0.263	180	4.572	4.82E-06	4.07E-02
rs11201470	10	86966910	C	T	0.26	179	4.599	4.25E-06	3.54E-02
rs11201472	10	86967515	G	A	0.263	180	4.56	5.12E-06	4.24E-02
rs11201474	10	86967642	C	T	0.26	179	4.599	4.25E-06	3.54E-02
rs11201475	10	86967680	T	G	0.26	179	4.599	4.25E-06	3.54E-02
rs11201477	10	86968052	G	T	0.26	179	4.599	4.25E-06	3.54E-02
rs11201478	10	86968139	A	T	0.26	179	4.599	4.25E-06	3.54E-02
rs11201479	10	86968244	T	A	0.26	179	4.599	4.25E-06	3.54E-02
rs12355989	10	86968359	C	T	0.261	178	4.539	5.65E-06	3.56E-02
rs12356318	10	86968645	C	T	0.26	179	4.599	4.25E-06	3.54E-02
rs12356001	10	86968652	G	A	0.263	180	4.572	4.82E-06	4.07E-02
rs12356002	10	86968663	G	A	0.263	180	4.572	4.82E-06	4.07E-02
rs34204566	10	86968897	C	T	0.26	179	4.599	4.25E-06	3.54E-02
rs61868038	10	86969069	T	C	0.26	179	4.599	4.25E-06	3.54E-02
rs61868039	10	86969134	C	T	0.26	179	4.599	4.25E-06	3.54E-02
rs11201480	10	86969555	C	G	0.261	179	4.599	4.25E-06	3.54E-02
rs11201481	10	86969674	T	A	0.26	179	4.599	4.25E-06	3.54E-02
rs11201482	10	86969788	C	A	0.261	179	4.599	4.25E-06	3.54E-02
rs11201483	10	86970632	G	A	0.26	179	4.599	4.25E-06	3.54E-02
rs11201484	10	86970701	T	A	0.26	178	4.582	4.61E-06	3.09E-02
rs12781036	10	86971053	C	T	0.26	179	4.599	4.25E-06	3.54E-02
rs12356962	10	86971306	C	A	0.26	179	4.599	4.25E-06	3.54E-02
rs12355378	10	86971344	T	C	0.26	179	4.599	4.25E-06	3.54E-02
rs61868040	10	86971381	G	T	0.331	210	4.739	2.15E-06	3.15E-02
rs11201485	10	86972270	G	A	0.26	179	4.599	4.25E-06	3.54E-02
rs12774986	10	86972939	C	G	0.26	179	4.599	4.25E-06	3.54E-02
rs7901089	10	86973061	G	A	0.331	210	4.739	2.15E-06	3.15E-02
rs12783552	10	86973422	C	T	0.26	179	4.599	4.25E-06	3.54E-02
rs7908060	10	86973494	C	T	0.318	202	4.724	2.31E-06	2.89E-02
rs7908084	10	86973539	G	T	0.324	205	4.959	7.09E-07	1.94E-02
rs12783023	10	86973709	A	C	0.26	179	4.599	4.25E-06	3.54E-02
rs12783994	10	86973858	G	A	0.26	179	4.599	4.25E-06	3.54E-02
rs12764867	10	86973880	C	T	0.26	179	4.599	4.25E-06	3.54E-02
rs11201486	10	86974335	T	C	0.26	179	4.599	4.25E-06	3.54E-02
rs11201489	10	86975054	A	G	0.26	179	4.599	4.25E-06	3.54E-02
rs11201490	10	86975061	T	C	0.26	179	4.599	4.25E-06	3.54E-02
rs7474554	10	86975367	A	G	0.263	180	4.572	4.82E-06	4.07E-02
rs11511545	10	86976098	A	G	0.26	179	4.599	4.25E-06	3.54E-02
rs10887462	10	86976198	A	T	0.331	209	4.822	1.42E-06	2.99E-02
rs11517193	10	86978079	G	A	0.26	179	4.599	4.25E-06	3.54E-02
rs11201494	10	86980055	G	A	0.26	179	4.599	4.25E-06	3.54E-02
rs11201496	10	86981163	A	G	0.26	179	4.599	4.25E-06	3.54E-02
rs111192240	10	86982278	A	C	0.312	198	4.547	5.45E-06	2.74E-02

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rs11201499	10	86982364	T	C	0.312	198	4.547	5.45E-06	2.74E-02
rs11201500	10	86982458	T	C	0.312	198	4.547	5.45E-06	2.74E-02
rs11201502	10	86982746	T	C	0.312	198	4.547	5.45E-06	2.74E-02
rs11201503	10	86982831	A	G	0.315	199	4.547	5.44E-06	2.41E-02
rs2067733	10	86983016	C	A	0.33	209	4.822	1.42E-06	3.17E-02
rs2067732	10	86983112	T	C	0.26	179	4.599	4.25E-06	3.54E-02
rs2067731	10	86983200	A	G	0.312	198	4.547	5.45E-06	2.74E-02
rs4326730	10	86983585	A	T	0.312	198	4.547	5.45E-06	2.74E-02
rs12357940	10	86983849	G	A	0.319	200	4.722	2.33E-06	6.99E-03
rs11201504	10	86984037	G	A	0.36	215	4.483	7.36E-06	2.79E-02
rs12258780	10	86984107	C	T	0.367	216	4.431	9.40E-06	4.20E-02
rs12766108	10	86984146	A	G	0.264	179	4.586	4.53E-06	8.13E-03
rs11201506	10	86984840	G	A	0.233	172	4.567	4.95E-06	7.27E-03
rs11201507	10	86984850	C	T	0.267	181	4.626	3.73E-06	1.80E-02
rs4751781	10	122104137	T	C	0.393	233	4.426	9.59E-06	4.89E-02
rs2420699	10	122105511	A	G	0.39	232	4.545	5.50E-06	3.34E-02
rs7085764	10	122110415	G	C	0.399	232	4.427	9.53E-06	3.33E-02
rs6585614	10	122110656	C	T	0.398	234	4.544	5.51E-06	3.76E-02
rs2901228	10	122115383	C	T	0.394	234	4.536	5.72E-06	5.72E-02
rs12799339	11	134683177	C	T	0.11	102	4.687	2.78E-06	3.98E-02
rs12804167	11	134683957	T	C	0.115	103	4.566	4.96E-06	6.64E-02
rs34965705	11	134683990	C	T	0.116	103	4.86	1.17E-06	2.99E-02
rs12804688	11	134684090	A	G	0.116	103	4.86	1.17E-06	2.99E-02
rs12786926	11	134684259	C	T	0.119	104	4.795	1.63E-06	3.23E-02
rs12785284	11	134684267	C	A	0.116	103	4.86	1.17E-06	2.99E-02
rs11819898	11	134684869	T	C	0.116	103	4.86	1.17E-06	2.99E-02
rs12786906	11	134684914	A	C	0.11	102	4.687	2.78E-06	3.98E-02
rs9576221	13	37789779	C	T	0.368	215	-4.591	4.41E-06	2.61E-02
rs9576222	13	37789910	C	T	0.366	214	-4.556	5.21E-06	2.75E-02
rs9566196	13	37789957	A	G	0.368	215	-4.591	4.41E-06	2.61E-02
rs10507446	13	37790007	A	G	0.366	214	-4.556	5.21E-06	2.75E-02
rs12585471	13	37791778	T	G	0.368	215	-4.591	4.41E-06	2.61E-02
rs12585465	13	37791815	T	C	0.368	215	-4.591	4.41E-06	2.61E-02
rs12583869	13	37791872	G	A	0.366	213	-4.527	5.98E-06	2.79E-02
rs76262092	13	37795449	G	A	0.366	214	-4.556	5.21E-06	2.75E-02
rs2181793	13	37797955	C	A	0.368	215	-4.591	4.41E-06	2.61E-02
rs9576223	13	37803027	G	A	0.368	215	-4.591	4.41E-06	2.61E-02
rs1324032	13	37807141	C	A	0.368	215	-4.591	4.41E-06	2.61E-02
rs1324033	13	37807152	C	T	0.373	218	-4.515	6.32E-06	2.78E-02
rs17055165	13	37810722	T	G	0.367	215	-4.66	3.16E-06	2.32E-02
rs2057533	13	37811007	T	A	0.366	213	-4.573	4.80E-06	2.72E-02
rs17055167	13	37812291	T	C	0.368	215	-4.591	4.41E-06	2.61E-02
rs9576227	13	37816214	C	T	0.367	215	-4.619	3.86E-06	2.92E-02
rs9566199	13	37818192	T	A	0.371	215	-4.555	5.24E-06	2.99E-02
rs150838167	17	13157439	C	T	0.098	98	4.46	8.19E-06	1.48E-01
rs3899359	17	13179734	G	A	0.088	88	4.66	3.17E-06	1.98E-01
rs174823	21	24489048	C	G	0.288	184	-4.472	7.76E-06	2.16E-02

*Adjusted for gender, age and height. MAF: Minor Allele Frequency, NINFF: Number of informative families

e-Table 4. The table shows all SNPs with association p-value below 10^{-5} for PB FEV1 (unadjusted) and the corresponding p-values for the adjusted trait.

rs ID	Chr	Basepair	A1	A2	MAF	NINFF	Z-score	unadjusted model p-value	adjusted model p-value
rs5779191	1	183818218	T	A	0.256	175	4.61	4.04E-06	5.21E-01
rs1978647	2	43371360	C	G	0.078	77	-4.469	7.87E-06	9.67E-02
rs6788345	3	130328243	T	G	0.502	205	-4.428	9.50E-06	1.42E-01
rs6439251	3	130333768	G	A	0.458	213	4.678	2.90E-06	7.62E-02
rs13322828	3	130336776	A	T	0.467	209	4.433	9.31E-06	6.91E-02
rs59630925	3	130337197	T	A	0.467	209	4.433	9.31E-06	6.91E-02
rs7651359	3	130339246	A	T	0.48	209	4.473	7.71E-06	9.64E-02
rs9849240	3	130354824	C	T	0.473	207	4.53	5.89E-06	7.76E-02
rs28623596	3	130356163	G	T	0.473	207	4.53	5.89E-06	7.76E-02
rs111196893	3	130356238	A	T	0.473	207	4.701	2.60E-06	7.59E-02
rs56857660	3	130357080	C	T	0.473	208	4.515	6.35E-06	8.08E-02
rs58456232	3	130357248	C	A	0.473	208	4.515	6.35E-06	8.08E-02
rs1484937	3	130357328	C	T	0.473	208	4.515	6.35E-06	8.08E-02
rs1484938	3	130357428	T	C	0.473	208	4.515	6.35E-06	8.08E-02
rs57114953	3	130357543	C	A	0.473	208	4.515	6.35E-06	8.08E-02
3:130357547:T:G	3	130357547	T	G	0.473	208	4.515	6.35E-06	8.08E-02
rs9858810	3	130358109	G	A	0.473	208	4.515	6.35E-06	8.08E-02
rs9821794	3	130358313	A	G	0.473	208	4.515	6.35E-06	8.08E-02
rs9821658	3	130358358	A	C	0.473	208	4.515	6.35E-06	8.08E-02
rs9821660	3	130358365	G	C	0.473	208	4.515	6.35E-06	8.08E-02
rs6791113	3	130358495	C	T	0.474	208	4.442	8.91E-06	9.49E-02
rs6778250	3	130358602	A	G	0.473	208	4.515	6.35E-06	8.08E-02
rs62418430	6	92355806	A	G	0.146	122	-4.414	1.00E-05	2.17E-02
rs7740935	6	163559154	A	T	0.143	125	-4.473	7.70E-06	7.15E-02
rs6924563	6	163560038	T	C	0.137	123	-4.55	5.36E-06	5.92E-02
rs10081348	7	156375728	T	C	0.049	56	4.408	1.00E-05	4.84E-01
rs10278648	7	156382240	T	C	0.1	112	4.468	7.89E-06	3.20E-01
rs13312612	7	156383684	A	G	0.1	112	4.468	7.89E-06	3.20E-01
rs1544525	7	156395110	C	G	0.1	112	4.468	7.89E-06	3.20E-01
rs62517707	8	131408202	A	G	0.238	176	4.82	1.43E-06	1.84E-02
rs72761264	9	133072737	A	G	0.132	107	-4.486	7.25E-06	9.40E-03
rs11593943	10	33545081	T	C	0.255	180	4.54	5.64E-06	8.99E-01
rs7901385	10	43337057	G	A	0.47	229	4.462	8.11E-06	4.12E-02
rs11201438	10	86942568	A	G	0.257	176	4.484	7.34E-06	5.55E-02
rs1339907	10	86950656	T	C	0.262	178	4.609	4.06E-06	2.37E-02
rs1339908	10	86950658	T	C	0.262	178	4.609	4.06E-06	2.37E-02
rs11201447	10	86955624	T	C	0.295	193	4.478	7.53E-06	6.58E-02
rs2050795	10	86957751	C	T	0.295	193	4.478	7.53E-06	6.58E-02
rs1339914	10	86960054	A	T	0.268	184	4.422	9.76E-06	1.19E-01
rs1339915	10	86960078	T	C	0.268	184	4.422	9.76E-06	1.19E-01
rs12766774	10	86960524	G	A	0.268	184	4.422	9.76E-06	1.19E-01
rs12766218	10	86960634	T	C	0.268	184	4.422	9.76E-06	1.19E-01
rs11201452	10	86961299	A	T	0.268	184	4.422	9.76E-06	1.19E-01
rs12768920	10	86962827	G	A	0.268	184	4.422	9.76E-06	1.19E-01
rs11201453	10	86963611	C	T	0.268	184	4.422	9.76E-06	1.19E-01
rs1416924	10	86964119	C	T	0.268	184	4.422	9.76E-06	1.19E-01



rs12777141	10	86964444	G	A	0.268	184	4.422	9.76E-06	1.19E-01
rs11201454	10	86964566	C	A	0.268	184	4.422	9.76E-06	1.19E-01
rs11201455	10	86964789	T	C	0.268	184	4.422	9.76E-06	1.19E-01
rs1416925	10	86964927	C	T	0.268	184	4.422	9.76E-06	1.19E-01
rs1416926	10	86965064	A	T	0.268	184	4.422	9.76E-06	1.19E-01
rs1416927	10	86965204	G	A	0.268	184	4.422	9.76E-06	1.19E-01
rs1416929	10	86965265	A	G	0.268	184	4.422	9.76E-06	1.19E-01
rs11201456	10	86965535	G	A	0.268	184	4.422	9.76E-06	1.19E-01
rs11201457	10	86965572	G	C	0.268	184	4.422	9.76E-06	1.19E-01
rs11201459	10	86966069	C	T	0.26	178	4.437	9.12E-06	6.52E-02
rs11201461	10	86966202	G	A	0.26	178	4.437	9.12E-06	6.52E-02
rs11201462	10	86966316	C	A	0.26	178	4.437	9.12E-06	6.52E-02
rs11201463	10	86966361	G	T	0.26	178	4.437	9.12E-06	6.52E-02
rs11201464	10	86966369	A	G	0.26	178	4.437	9.12E-06	6.52E-02
rs11201465	10	86966491	C	T	0.26	178	4.437	9.12E-06	6.52E-02
rs11201466	10	86966577	T	A	0.26	178	4.437	9.12E-06	6.52E-02
rs11201467	10	86966590	G	A	0.26	178	4.437	9.12E-06	6.52E-02
rs11201468	10	86966732	T	C	0.26	178	4.437	9.12E-06	6.52E-02
rs11201469	10	86966777	T	C	0.263	179	4.501	6.75E-06	7.33E-02
rs11201470	10	86966910	C	T	0.26	178	4.437	9.12E-06	6.52E-02
rs11201472	10	86967515	G	A	0.263	179	4.48	7.47E-06	7.56E-02
rs11201474	10	86967642	C	T	0.26	178	4.437	9.12E-06	6.52E-02
rs11201475	10	86967680	T	G	0.26	178	4.437	9.12E-06	6.52E-02
rs11201477	10	86968052	G	T	0.26	178	4.437	9.12E-06	6.52E-02
rs11201478	10	86968139	A	T	0.26	178	4.437	9.12E-06	6.52E-02
rs11201479	10	86968244	T	A	0.26	178	4.437	9.12E-06	6.52E-02
rs12356318	10	86968645	C	T	0.26	178	4.437	9.12E-06	6.52E-02
rs12356001	10	86968652	G	A	0.263	179	4.501	6.75E-06	7.33E-02
rs12356002	10	86968663	G	A	0.263	179	4.501	6.75E-06	7.33E-02
rs34204566	10	86968897	C	T	0.26	178	4.437	9.12E-06	6.52E-02
rs61868038	10	86969069	T	C	0.26	178	4.437	9.12E-06	6.52E-02
rs61868039	10	86969134	C	T	0.26	178	4.437	9.12E-06	6.52E-02
rs11201480	10	86969555	C	G	0.261	178	4.437	9.12E-06	6.52E-02
rs11201481	10	86969674	T	A	0.26	178	4.437	9.12E-06	6.52E-02
rs11201482	10	86969788	C	A	0.261	178	4.437	9.12E-06	6.52E-02
rs11201483	10	86970632	G	A	0.26	178	4.437	9.12E-06	6.52E-02
rs11201484	10	86970701	T	A	0.26	177	4.427	9.53E-06	5.45E-02
rs12781036	10	86971053	C	T	0.26	178	4.437	9.12E-06	6.52E-02
rs12356962	10	86971306	C	A	0.26	178	4.437	9.12E-06	6.52E-02
rs12355378	10	86971344	T	C	0.26	178	4.437	9.12E-06	6.52E-02
rs61868040	10	86971381	G	T	0.331	209	4.581	4.63E-06	4.03E-02
rs11201485	10	86972270	G	A	0.26	178	4.437	9.12E-06	6.52E-02
rs12774986	10	86972939	C	G	0.26	178	4.437	9.12E-06	6.52E-02
rs7901089	10	86973061	G	A	0.331	209	4.581	4.63E-06	4.03E-02
rs12783552	10	86973422	C	T	0.26	178	4.437	9.12E-06	6.52E-02
rs7908060	10	86973494	C	T	0.318	201	4.528	5.97E-06	3.46E-02
rs7908084	10	86973539	G	T	0.324	204	4.758	1.95E-06	2.18E-02
rs12783023	10	86973709	A	C	0.26	178	4.437	9.12E-06	6.52E-02
rs12783994	10	86973858	G	A	0.26	178	4.437	9.12E-06	6.52E-02
rs12764867	10	86973880	C	T	0.26	178	4.437	9.12E-06	6.52E-02
rs11201486	10	86974335	T	C	0.26	178	4.437	9.12E-06	6.52E-02
rs11201489	10	86975054	A	G	0.26	178	4.437	9.12E-06	6.52E-02

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rs11201490	10	86975061	T	C	0.26	178	4.437	9.12E-06	6.52E-02
rs7474554	10	86975367	A	G	0.263	179	4.501	6.75E-06	7.33E-02
rs11511545	10	86976098	A	G	0.26	178	4.437	9.12E-06	6.52E-02
rs10887462	10	86976198	A	T	0.331	208	4.649	3.34E-06	4.06E-02
rs11517193	10	86978079	G	A	0.26	178	4.437	9.12E-06	6.52E-02
rs11201494	10	86980055	G	A	0.26	178	4.437	9.12E-06	6.52E-02
rs11201496	10	86981163	A	G	0.26	178	4.437	9.12E-06	6.52E-02
rs2067733	10	86983016	C	A	0.33	208	4.676	2.93E-06	3.88E-02
rs2067732	10	86983112	T	C	0.26	178	4.437	9.12E-06	6.52E-02
rs12357940	10	86983849	G	A	0.319	199	4.423	9.75E-06	8.28E-03
rs11201504	10	86984037	G	A	0.36	214	4.441	8.97E-06	2.10E-02
rs11201507	10	86984850	C	T	0.267	180	4.41	1.00E-05	4.30E-02
rs2420699	10	122105511	A	G	0.39	231	4.428	9.53E-06	2.53E-02
rs2901228	10	122115383	C	T	0.394	233	4.446	8.75E-06	3.89E-02
rs34965705	11	134683990	C	T	0.116	102	4.546	5.47E-06	1.72E-02
rs12804688	11	134684090	A	G	0.116	102	4.546	5.47E-06	1.72E-02
rs12786926	11	134684259	C	T	0.119	103	4.481	7.45E-06	1.90E-02
rs12785284	11	134684267	C	A	0.116	102	4.546	5.47E-06	1.72E-02
rs11819898	11	134684869	T	C	0.116	102	4.546	5.47E-06	1.72E-02
rs10860615	12	101023679	G	A	0.386	211	-4.427	9.55E-06	2.73E-01
rs522097	13	26748748	A	G	0.199	160	4.525	6.04E-06	2.25E-01
rs9576218	13	37785892	T	C	0.41	222	-4.426	9.62E-06	1.26E-02
rs9576221	13	37789779	C	T	0.368	214	-5.054	4.33E-07	4.46E-03
rs9576222	13	37789910	C	T	0.366	213	-5.022	5.11E-07	4.61E-03
rs9566196	13	37789957	A	G	0.368	214	-5.054	4.33E-07	4.46E-03
rs10507446	13	37790007	A	G	0.366	213	-5.022	5.11E-07	4.61E-03
rs12585471	13	37791778	T	G	0.368	214	-5.054	4.33E-07	4.46E-03
rs12585465	13	37791815	T	C	0.368	214	-5.054	4.33E-07	4.46E-03
rs12583869	13	37791872	G	A	0.366	212	-4.986	6.17E-07	4.93E-03
rs76262092	13	37795449	G	A	0.366	213	-5.022	5.11E-07	4.61E-03
rs2181793	13	37797955	C	A	0.368	214	-5.054	4.33E-07	4.46E-03
rs9576223	13	37803027	G	A	0.368	214	-5.054	4.33E-07	4.46E-03
rs1324032	13	37807141	C	A	0.368	214	-5.054	4.33E-07	4.46E-03
rs1324033	13	37807152	C	T	0.373	217	-4.993	5.95E-07	4.54E-03
rs17055165	13	37810722	T	G	0.367	214	-5.122	3.03E-07	3.92E-03
rs2057533	13	37811007	T	A	0.366	212	-5.04	4.67E-07	4.54E-03
rs17055167	13	37812291	T	C	0.368	214	-5.054	4.33E-07	4.46E-03
rs9576227	13	37816214	C	T	0.367	214	-5.085	3.69E-07	4.95E-03
rs9566199	13	37818192	T	A	0.371	214	-5.029	4.93E-07	4.87E-03
rs9576228	13	37819029	G	A	0.337	206	-4.761	1.93E-06	1.16E-02
rs4143038	13	37820805	A	G	0.335	204	-4.785	1.71E-06	1.27E-02
rs9576231	13	37834559	G	A	0.335	204	-4.785	1.71E-06	1.27E-02
rs150838167	17	13157439	C	T	0.098	97	4.571	4.86E-06	1.27E-01
rs3899359	17	13179734	G	A	0.088	87	4.764	1.89E-06	2.02E-01

*Adjusted for gender, age and height. MAF: Minor Allele Frequency, NINFF: Number of informative families

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