ONLINE REPOSITORY

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POPULATION CHARACTERISTICS

Severe asthma case cohorts

The Asthma UK Genetics of Severe Asthma (AUGOSA) Study

This study consists of 750 individuals of European ancestry with severe asthma classified as steps 3 or above based on the Global Initiative for Asthma (GINA) criteria recruited across 8 UK-based centres: Nottingham QMC, Nottingham City Hospital, Belfast, Glasgow, Leicester, Manchester, Birmingham, and Southampton. Analyses included 682 individuals recruited for the AUGOSA study. Subjects from Belfast, Glasgow, Leicester and Manchester fulfilled the American Thoracic Society (ATS) definition of refractory asthma and were recruited as part of the British Thoracic Society (BTS) National Difficult Asthma Registry [1]. Clinical characteristics for subjects from each centre are described below.

Nottingham QMC, Nottingham City Hospital:

A total of 149 individuals were recruited from Nottingham QMC and Nottingham City Hospital, of which 57.3% were female. All individuals had a physician diagnosis of severe asthma and were judged to be at GINA criteria step 3 or above. The mean age was 39.8 years (SD 11.8, range 16–62) and the age of onset of asthma was ≤16 years in 53.7%. The mean FEV1 was 2.61L (SD 0.8) and the mean % predicted FEV1 was 83.2% (SD 22.8). In this population, 13.4% were lifetime smokers and 9.4% were current smokers.

Belfast:

A total of 99 individuals were recruited from Belfast City Hospital, of which 61.6% were

female. All individuals had a physician diagnosis of severe asthma and required treatment at step 4/5 of BTS/SIGN guideline [2]. The mean age was 48.6 years (SD 12.6, range 18–78) and the age of onset of asthma was ≤16 years in 47.2%. The mean FEV1 was 2.1L (SD 0.73) and the mean % predicted FEV1 was 74.4% (SD 24.4). In this population, 65.7% were never smokers, 31.3% were ex-smokers, & 3% were current smokers.

Glasgow:

A total of 249 individuals were recruited from Glasgow, of which 62.2% were female. All individuals had a physician diagnosis of asthma and were judged to be at GINA criteria step 3 or above. The mean age was 51.8 years (SD 12.8, range 18-85) and the age of onset of asthma was ≤16 years in 58.4%. The mean FEV1 was 1.98L (SD 0.8) and the mean % predicted FEV1 was 70.6% (SD 21.5). In this population, 49.4% were never smokers, 12.6% ever smokers and 38.0% were current smokers.

Leicester:

A total of 63 individuals were recruited from The Institute for Lung Health, University of Leicester, of which 79% were female. All individuals had a physician diagnosis of severe asthma and were judged to be at GINA criteria step 3 (18%), 4 (48%) or 5 (34%). The mean age was 47 years (SD 17) and the age of onset of asthma was ≤16 years in 39.7%. The mean FEV1 was 2.4L (SD 0.9) and the mean % predicted FEV1 was 78% (SD 22). In this population, 17% were current smokers and a further 5% were ever smokers (>10 pack year history).

Manchester:

A total of 65 individuals (69% females) were recruited by the Manchester Academic Health Science Centre. All individuals had a physician diagnosis of severe asthma and were judged to be at GINA criteria step 3 or above. The mean age was 45.7 years (SD 12.8) and the age of onset of asthma was ≤16 years in 47.1%. The mean FEV1 was 1.97L (SD 0.9) and the mean % predicted FEV1 was 67% (SD 29). In this population, 32% were lifetime smokers and 11% were current smokers.

Birmingham:

A total of 47 individuals (15% males) were recruited from Birmingham Heartlands Hospital. All individuals were put through a specialist clinic structured severe asthma protocol and had a physician diagnosis of severe asthma and were judged to be at GINA criteria step 4 or above (70% were on maintenance or intermittent oral corticosteroids treatment). The mean age was 44.6 years (range 16–71) and the age of onset of asthma was ≤16 years in 59.2%. The mean FEV1 was 1.95L (SD=0.88) and the mean % predicted FEV1 was 56.7% (SD=28). In this population, 20.5% were lifetime smokers and 2.5% were current smokers."

Southampton:

A total of 78 individuals were recruited from Southampton General Hospital of which 75.6% were female. All individuals had a physician diagnosis of severe asthma and were managed at step 4/5 of the BTS/SIGN guidelines [2]. Their mean age was 42.7 years (SD 12.1, range 17–74) and the age of onset of asthma was ≤16 years in 50.1%. The mean FEV1 was 2.04L (SD 0.7) and the mean % predicted FEV1 was 69.3% (SD 19.1). In this population, 29.9% were lifetime smokers and 15.6% were current smokers.

A further 344 individuals with severe asthma were recruited from three specialist asthma clinics; adult and childhood clinics based at the Royal Brompton Hospital, London and an adult clinic at the Glenfield Hospital, Leicester. Patients attending the Glenfield Hospital clinics had full characterisation and were deemed to have severe/refractory asthma according to a specialised protocol involving parameters of airway inflammation, airway physiology, as well as quality of life and control of symptoms [2, 3]. Those attending Royal Brompton Hospital adult clinics were also fully characterised, with severe asthma defined according to the ATS and ERS definition of severe asthma [4, 5].

Severe asthma in the paediatric clinic was defined as one or more of the following criteria: (1) Persistent (most days, for at least 3 months) chronic symptoms (the necessity because of symptoms for short-acting β2 agonists at least three times/week) of airways obstruction despite high dose inhaled corticosteroids (Beclomethasone equivalent 800 mcg/day) and trials of every add-on medication available in the country of residence (these would include, if available, long acting β2 agonist, leukotriene receptor antagonist, oral theophylline in the low, anti-inflammatory dose). This group includes Type 1 brittle asthma. (2) Recurrent severe asthma exacerbations despite attempts with medication including trials of allergen avoidance, low dose daily inhaled corticosteroids or intermittent high dose inhaled corticosteroids: *either* at least one admission to an intensive care unit, or at least two hospital admissions requiring intravenous medication/s, *or* $\geq$2 courses of oral steroids during the last year, despite the above therapy. This group includes Type 2 brittle asthma. (3) Persistent airflow obstruction: post oral steroid, post-bronchodilator Z score <-1.96 for FEV_1, with appropriate normative data despite the above therapy. (4) The necessity of prescription of alternate day or daily oral steroids to achieve control of asthma. Children were evaluated in detail to exclude as far as possible non-adherence to therapy, significant co-morbidity (for example, rhinosinusitis and

147 gastroesophageal reflux), psychosocial issues and adverse environmental circumstances as
148 contributing factors to the severity of asthma [5-8].
149
150 The primary analysis dataset of 1,059 cases and 3,345 controls had 80% power ($\alpha = 0.05$) to
151 detect an OR of approximately 1.19 for a SNP with MAF 10%; 1.14 for a SNP with MAF
152 25%; and 1.12 for a SNP with MAF 40%.
153
154 **Replication Cohort**
155 *Australian Asthma Genetics Consortium (AAGC) study*
156 This study includes 7,197 unrelated individuals of European ancestry from Australia. Of
157 these, we selected for the present analysis 231 cases recruited by the Lung Institute of
158 Western Australia (LIWA) who (a) were diagnosed with asthma by clinical examination by a
159 respiratory physician and (b) were on inhaled steroids at 400μg or higher plus a LABA. All
160 recruited subjects had a <10 pack year smoking history. In addition all patients were
161 interviewed by a chest physician, had spirometry and reversibility and/or bronchial reactivity
162 measured. They also had a clinical history compatible with asthma including a history of
163 variability and exacerbations from common asthma triggers. Clinical characteristics for these
164 subjects are summarised in Table E1. All samples were genotyped with Illumina 610K
165 arrays.
166
167 **AAGC samples included in the follow-up analysis.**

Attribute	Asthma cases	Asthma controls
N	231	1345
% Female	61.0	60.6
Mean age (SD, range)	51 (16.3, 11-87)	32 (15.0, 12-89)
% with family history of asthma	65.3	0
% SPT+	85.7	-
% Asthma onset <= 16 years	54.5	-

Mean FEV1, L (SD)	2.21 (0.88)	-
Mean FVC, L (SD)	3.23 (1.09)	-
Mean FEV1/FVC (SD)	0.68 (0.13)	-
% lifetime smoker	48.1	-
% current smoker	7.4	-
% ever admitted to hospital for asthma	53.7	-

We restricted our analysis to 1,345 asthma-free controls also genotyped with 610K arrays recruited through two studies: LIWA (n=35) and the Queensland Institute of Medical Research (QIMR) studies (n=1,310). The latter reported never having had asthma in questionnaires completed as part of five epidemiological studies previously conducted at QIMR and described in more detail elsewhere [9]. All subjects were confirmed to be unrelated and of European ancestry through the analysis of genome-wide allele sharing.

Standard SNP QC filters were applied, including the removal of SNPs with call rate <95%, minor allele frequency (MAF) < 0.01 and Hardy-Weinberg equilibrium test *P*-value < 10^{-6}. Autosomal SNPs passing QC were then used to impute up to 7.8 million variants available from the combined 1000 Genomes (CEU, Mar 2010 release) and HapMap 3 (all 11 populations, Feb 2009 release) reference panels using Impute2 [10]. After imputation, we excluded SNPs with low imputation accuracy (information < 0.3), MAF < 0.01, Hardy-Weinberg equilibrium test *P*-value < 10^{-6}. After QC, genotype data was for 5.7 million SNPs that were tested for association using a standard case-control allelic test. The genomic inflation factor for this analysis was 1.019.

The replication cohort dataset of 231 cases and 1,345 controls had 80% power to detect an OR 1.46 (MAF=10%), 1.31 (MAF=25%), and 1.28 (MAF=40%).

For the severe versus mild analyses, a total of 1,085 mild asthmatics were identified as having never received steroid medication in their lifetime.

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TABLE E1

	Platform	SNP markers	Samples
Cases			
AUGOSA 610	llumina 610K	582,892	113
AUGOSA 660	llumina 660W	557,124	530
GABRIEL	llumina 610K	582,892	290
`otal			**933**
Controls			
3HS	llumina 610K	82,892	65
VTCCC2	llumina 1.2M	,157,986	481
`1DGC	llumina 550K	61,303	300
`otal			**346**
SNPs in common		90,303	

Samples genotyped on each platform.

FIG E1

Principal components analysis (PCA) of study populations was carried out to correct for population structure based on the covariance of effect allele loadings on a representative sample of 57,213 SNPs in low LD using EIGENSOFT. A) No clear separation of clusters for each cohort suggests homogeneous populations. B) The PCA analysis identified 119 outliers with variances >6σ.

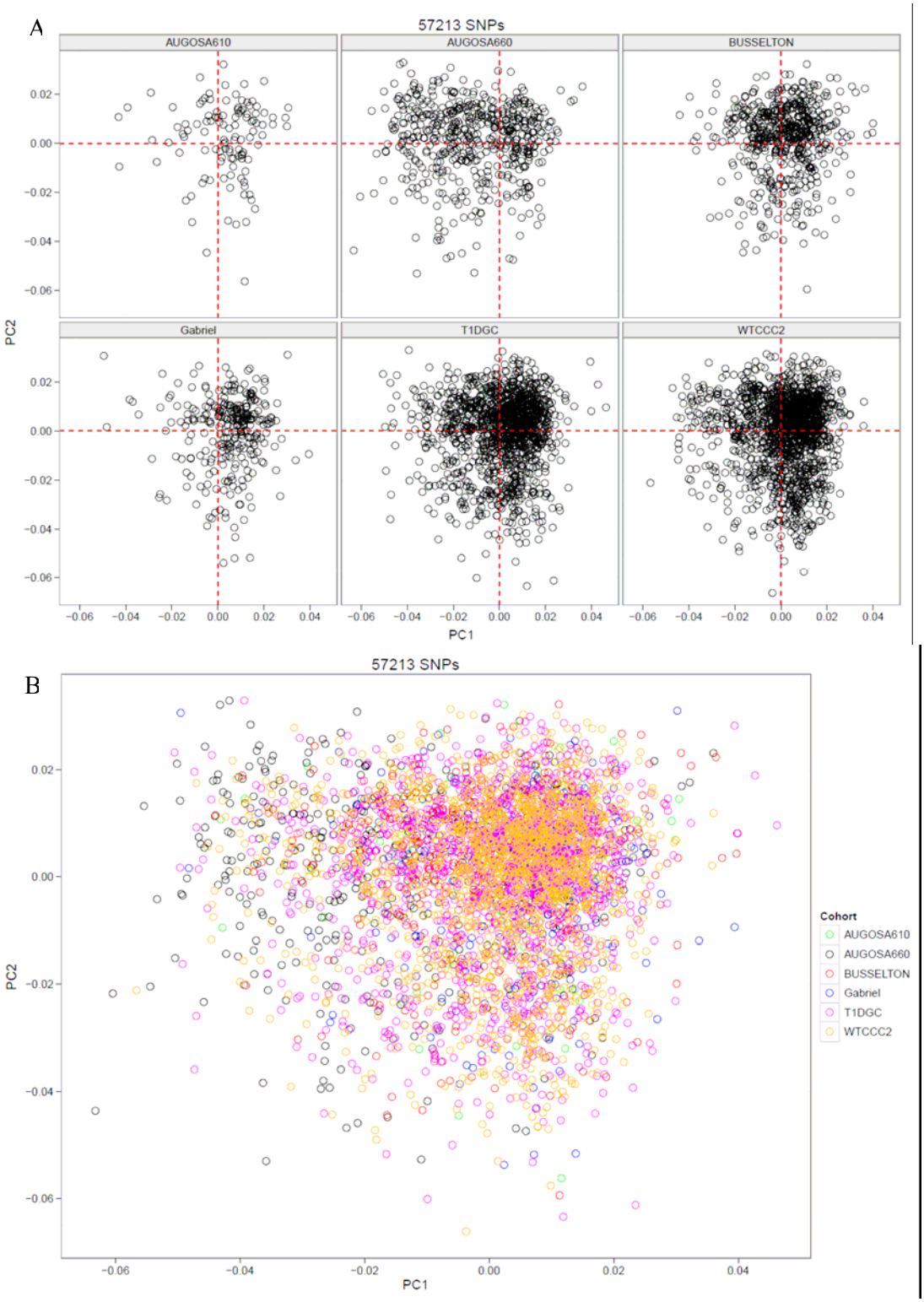

A
57213 SNPs
AUGOSA610
AUGOSA660
BUSSELTON
Gabriel
T1DGC
WTCCC2
PC2
PC1
B
57213 SNPs
PC2
PC1
Cohort
AUGOSA610
AUGOSA660
BUSSELTON
Gabriel
T1DGC
WTCCC2

TABLE E2

Location				AUGOSA (933 cases, 3,346 controls)				GABRIEL (10,365 cases 16,110 controls)			
Chr	Locus	SNP	Position	Ref	Alt	OR (95% CI)	P Value	Ref	Alt	OR (95% CI)	P Value
Genome-wide significant loci ($p \leq 7.2 \times 10^{-8}$) in the GABRIEL study											
2	IL18R1	rs3771166	102352654	G	A	0.79 (0.71-0.88)	1.93×10^{-5}	G	A	0.87 (0.83-0.91)	3.40×10^{-9}
6	HLA-DQ	rs9273349	32733847	-	-	-	-	T	C	1.18 (1.13-1.24)	7.00×10^{-14}
9	IL33	rs1342326	6180076	T	C	1.18 (1.03-1.35)	0.018	T	C	1.20 (1.13-1.28)	9.20×10^{-10}
15	SMAD3	rs744910	65233839	A	G	1.21 (1.09-1.35)	2.88×10^{-4}	G	A	0.89 (0.86-0.92)*	3.90×10^{-9}
17	GSDMB	rs2305480	35315722	G	A	0.80 (0.72-0.89)	5.56×10^{-5}	G	A	0.85 (0.81-0.90)	9.60×10^{-8}
17	GSDMA	rs3894194	35375519	G	A	1.25 (1.12-1.39)	4.39×10^{-5}	G	A	1.17 (1.11-1.23)	4.60×10^{-9}
22	IL2RB	rs2284033	35863980	G	A	0.92 (0.82-1.02)	0.105	G	A	0.89 (0.86-0.93)	1.20×10^{-8}
Suggestive loci ($p \leq 5 \times 10^{-7}$) in the GABRIEL study											
5	SLC22A5	rs2073643	131751187	C	T	1.15 (1.04-1.28)	0.009	T	C	0.90 (0.87-0.94)*	2.20×10^{-7}
5	IL13	rs1295686	132023742	C	T	1.29 (1.14-1.47)	9.30×10^{-5}	T	C	0.87 (0.83-0.92)*	1.40×10^{-7}
15	RORA	rs11071559	58857280	C	T	0.89 (0.76-1.05)	0.159	C	T	0.85 (0.80-0.90)	1.10×10^{-7}

* Opposite coding allele

Association results in AUGOSA of SNPs identified with significant or suggestive evidence of effects on the risk of asthma by the GABRIEL Consortium. Odds ratios were calculated by designating alternative alleles (Alt) as effect alleles. Ref denotes reference allele, Alt alternative allele and CI confidence interval. We were unable to test for association with the *HLA-DQ* locus due to reduced coverage on the Illumina genotyping platform, no proxy SNPs in LD were identified. The SNP in closest proximity was genotyped rs2187668 (32713862), p=0.26.

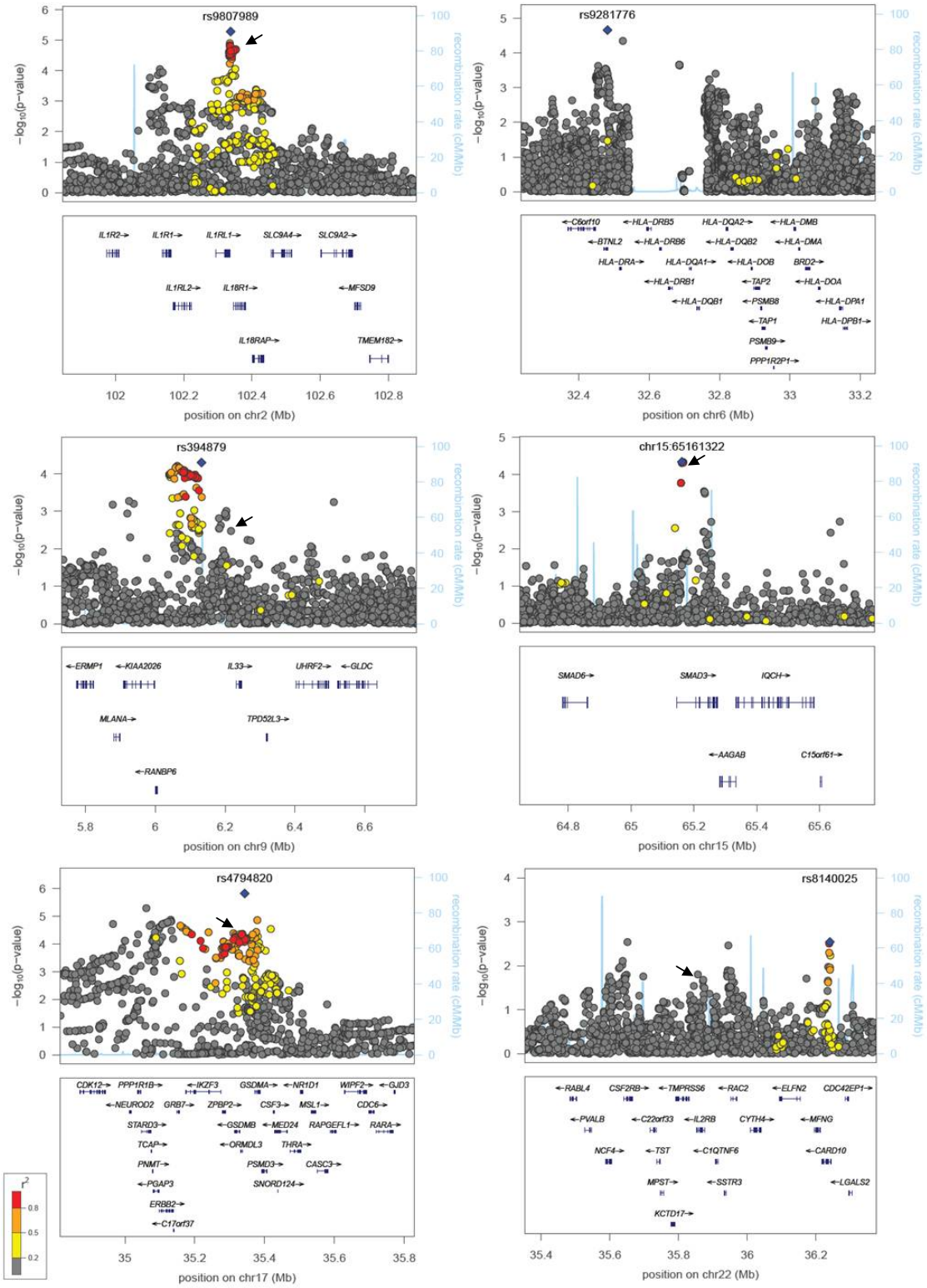
FIG E2

Regions plots were generated for the highest significance SNP in AUGOSA within GABRIEL identified loci (reported SNP ±500Kb), listed in Table E2.

The Region plots show the statistical significance of each SNP on the –log10 scale as a function of chromosome position (NCBI build 36). The pivotal SNP is shown in blue and the correlation (r^2) of each of the surrounding SNPs to the pivotal SNP is shown by their colour (see key). Fine scale recombination rate is plotted in blue. SNPs reported by GABRIEL are identified by the arrow shown.

We were unable to test for association with the *HLA-DQ* locus due to reduced coverage on the Illumina genotyping platform, no proxy SNPs in LD were identified.

Association results in AUGOSA of genome-wide significant loci ($p \leq 7.2x10^{(-8)}$) in the GABRIEL study



Association results in AUGOSA of suggestive loci ($p \leq 5x10^{(-7)}$) in the GABRIEL study

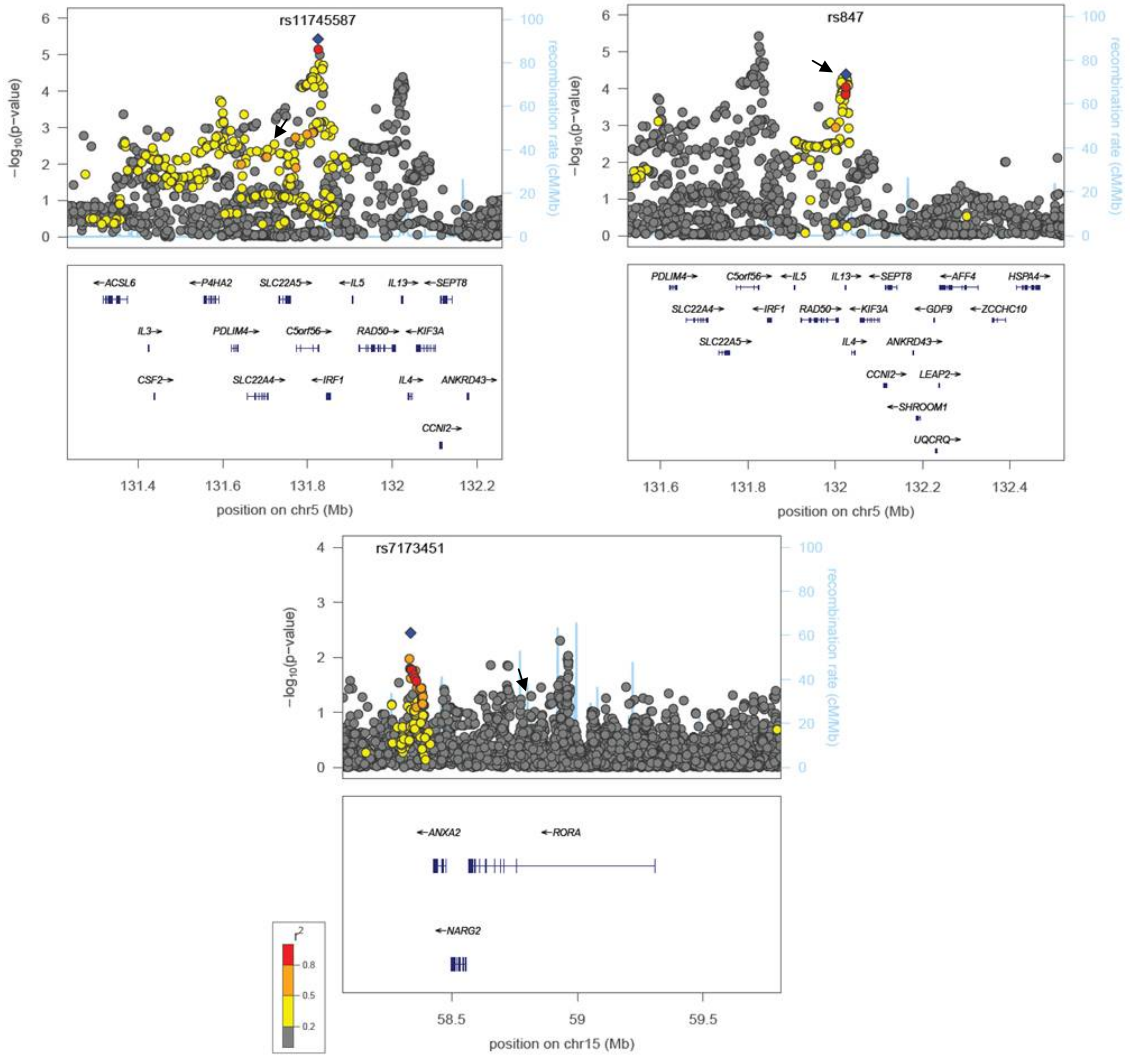


TABLE E3

Chr	Locus	GABRIEL SNP	AUGOSA top SNP in region (±500kb)	OR (95% CI)	P Value
Genome-wide significant loci ($p \leq 7.2x10^{(-8)}$) in the GABRIEL study					
2	IL18R1	rs3771166	rs9807989	0.76 (0.67-0.85)	$5.20x10^{(-6)}$
6	HLA-DQ	rs9273349	rs9281776	1.72 (1.34-2.22)	$2.18x10^{(-5)}$
9	IL33	rs1342326	rs394879	0.74 (0.64-0.86)	$5.01x10^{(-5)}$
15	SMAD3	rs744910	chr15:65161322	1.66 (1.30-2.11)	$4.61x10^{(-5)}$
17	GSDMB	rs2305480	rs4794820	0.76 (0.68-0.85)	$1.52x10^{(-6)}$
17	GSDMA	rs3894194	rs4794820	0.76 (0.68-0.85)	$1.52x10^{(-6)}$
22	IL2RB	rs2284033	**rs8140025**	**1.17 (1.06-1.30)**	**0.003**
Suggestive loci ($p \leq 5x10^{(-7)}$) in the GABRIEL study					
5	SLC22A5	rs2073643	**rs11745587**	**1.30 (1.17-1.45)**	**$2.09x10^{(-6)}$**
5	IL13	rs1295686	rs847	1.35 (1.17-1.55)	$4.05x10^{(-5)}$
15	RORA	rs11071559	rs7173451	0.85 (0.76-0.95)	0.004

Highest significance SNPs in AUGOSA within GABRIEL identified loci. Genotyped SNPs are shown in bold, imputed SNPs are shown in non-bold.

FIG E3

Quantile-Quantile plot and Manhattan plot of severe versus mild-to-moderate asthma results. A) Quantile-Quantile (Q-Q) plot showing GWA results for genotyped SNPs. The straight line shows the distribution of 488,809 SNPs analysed in 1,026 severe asthmatics and 1,028 mild asthmatics under the null hypothesis. B) Manhattan plot showing GWA results for 488,809 genotyped SNPs analysed in 1,026 severe asthmatics and 1,028 mild asthmatics under analysis.

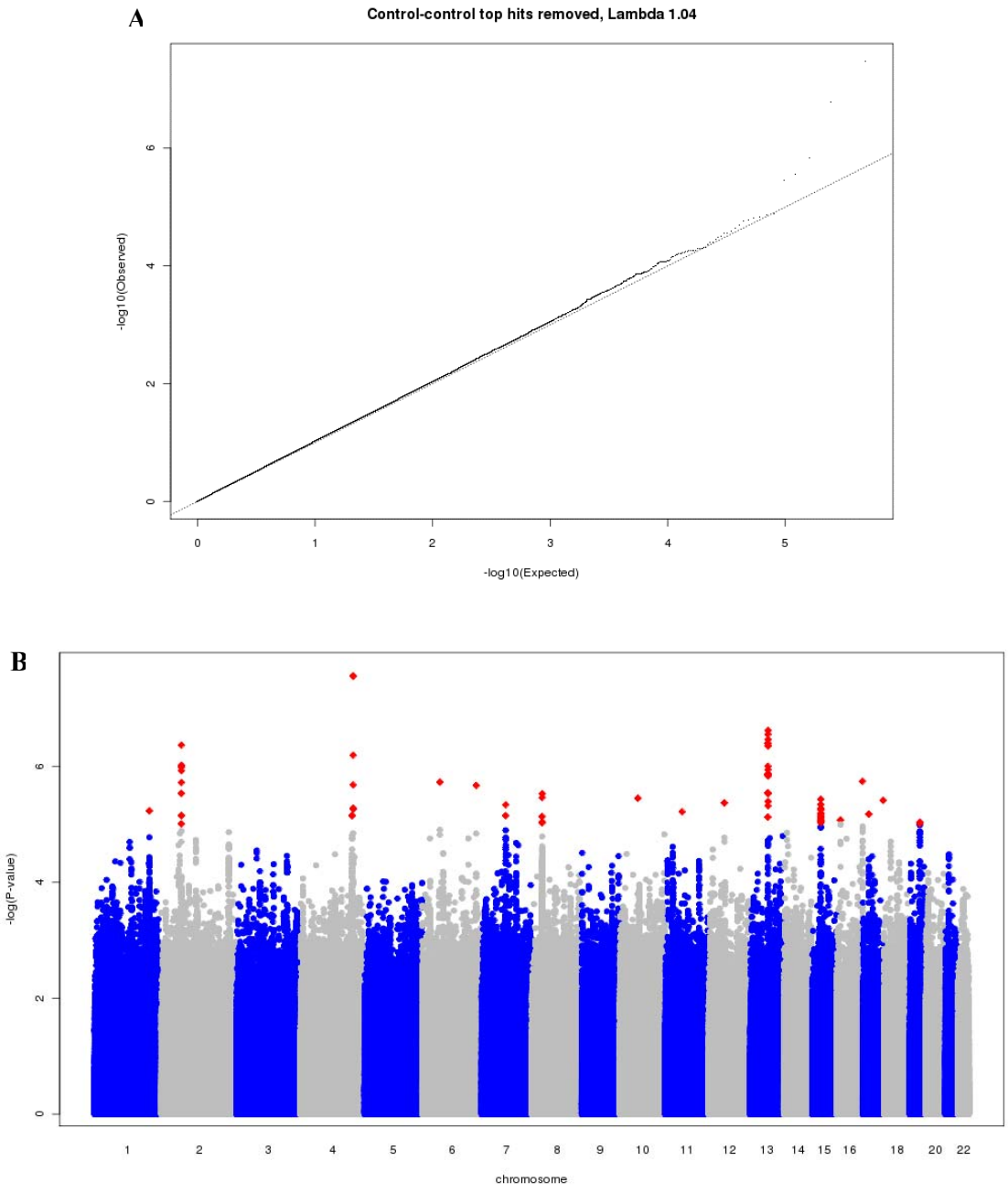


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TABLE E4

Chr	SNP	Position	A1	BETA	SE	OR (95% CI)	p value	Gene
5	rs1837253	110429771	T	-0.29	0.06	0.75(0.66-0.85)	$5.52x10^{(-6)}$	*TSLP* (upstream)
3	rs11711981	195373706	A	-0.23	0.05	0.80 (0.72-0.88)	$2.19x10^{(-5)}$	
13	rs1414320	109333093	C	0.35	0.08	1.42 (1.21-1.68)	$2.33x10^{(-5)}$	
2	rs333236	107970399	C	0.29	0.06	1.33 (1.18-1.51)	$6.47x10^{(-6)}$	*SLC5A7* (intronic)
16	rs8057431	83397455	G	-0.27	0.06	0.76 (0.67-0.86)	$1.20x10^{(-5)}$	
6	rs12200468	73408591	G	-0.31	0.07	0.73 (0.64-0.84)	$1.47x10^{(-5)}$	*KCNQ5* (intronic)
5	rs6876572	150719195	G	-0.28	0.06	0.76 (0.67-0.86)	$1.60x10^{(-5)}$	
1	rs6424762	78522496	G	-0.23	0.05	0.79 (0.71-0.88)	$1.70x10^{(-5)}$	
10	rs2068888	94829632	A	0.23	0.05	1.26 (1.13-1.40)	$2.12x10^{(-5)}$	
4	rs981516	161784820	A	0.24	0.06	1.27 (1.14-1.43)	$2.27x10^{(-5)}$	
2	rs896733	20682797	C	-0.28	0.07	0.75 (0.66-0.86)	$2.87x10^{(-5)}$	*HS1BP3* (intronic)
4	rs13150370	80106067	A	0.22	0.05	1.25 (1.13-1.39)	$3.05x10^{(-5)}$	
11	rs597872	107071795	A	-0.23	0.06	0.79 (0.71-0.88)	$3.08x10^{(-5)}$	
3	rs1343700	125054444	G	0.23	0.06	1.26 (1.13-1.40)	$3.20x10^{(-5)}$	*MYLK* (intronic)
8	rs4870880	125020708	C	-0.27	0.07	0.76 (0.67-0.87)	$3.25x10^{(-5)}$	*FER1L6* (intronic)
19	rs2241351	18294225	T	0.32	0.08	1.37 (1.18-1.60)	$3.50x10^{(-5)}$	*LSM4* (intronic)
1	rs6701588	171619782	T	0.30	0.07	1.35 (1.17-1.56)	$4.21x10^{(-5)}$	
20	rs2326614	5195393	C	0.23	0.06	1.25 (1.12-1.40)	$4.53x10^{(-5)}$	
11	rs7480563	1091649	T	0.22	0.05	1.24 (1.12-1.38)	$4.68x10^{(-5)}$	*MUC2* (missense)

Additional SNPs with $p< 5\times10^{-5}$ not already reported due to having no second supporting SNP with $p<5\times10^{-5}$.