

Letter to the Editor

The *C11orf30-LRRC32* region is associated with total serum IgE levels in asthmatic patients

To the Editor:

Asthma is a chronic inflammatory respiratory disease characterized by bronchial hyperresponsiveness, increased T_H2 cytokine levels, and increased serum IgE levels. Atopic dermatitis or eczema is a chronic inflammatory skin disease characterized by epidermal barrier dysfunction and IgE-mediated sensitization. The only published genome-wide association study (GWAS) of atopic dermatitis identified rs7927894 on chromosome 11q13.5 between the chromosome 11 open reading frame 30 (*C11orf30*) and leucine-rich repeat containing 32 (*LRRC32*) genes.¹ A replication study further confirmed the association of rs7927894 with childhood eczema.² The same variant is also associated with Crohn disease, an inflammatory bowel disease.³ Increased total serum IgE levels are common in both patients with asthma and those with eczema, and therefore we studied whether the *C11orf30-LRRC32* region is associated with total serum IgE levels and asthma in 3 independently ascertained non-Hispanic white populations: the National Heart, Lung, and Blood Institute (NHLBI)-funded Severe Asthma Research Program (SARP); the NHLBI's Collaborative Studies on the Genetics of Asthma (CSGA) studies; and the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) multicenter study. For additional information on the methods used, see the **Methods** section in this article's Online Repository at www.jacionline.org.

After quality control analysis, data from 1334 subjects (SARP plus CSGA patients with asthma, $n = 607$; SARP plus CSGA healthy control subjects, $n = 292$; and TENOR patients with asthma, $n = 435$) were analyzed either combined or separately for association with total serum IgE levels (see **Table E1** in this article's Online Repository at www.jacionline.org). Multiple testing was minimized because analysis was restricted to 25 single nucleotide polymorphisms (SNPs) covering the whole *C11orf30-LRRC32* region (P value for Bonferroni adjustment = .002, $P = .05/25$ SNPs).

Four SNPs (rs7130588, rs2508746, rs10899234, and rs6592657) were significantly associated with total serum IgE levels after multiple test adjustment (**Table I** and see **Fig E1** in this article's Online Repository at www.jacionline.org). rs7130588, approximately 8 kb downstream of *C11orf30*, showed the strongest association with total serum IgE levels ($P = .000034$), which remained significant after adjusting for asthma status ($P = .00021$, see **Table E2** in this article's Online Repository at www.jacionline.org) or positive skin test response status ($P = .033$, see **Table E3** in this article's Online Repository at www.jacionline.org). rs7130588 was marginally associated with skin prick test response status ($P = .080$, see **Table E3**). rs7130588 is in almost perfect linkage disequilibrium (LD; $r^2 = 0.97$), with the previous top SNP, rs7927894, identified from the GWAS of eczema.¹ SNPs rs2508746 and rs10899234 were also located at the 3' end of *C11orf30* and were in moderate ($r^2 = 0.60$) and mild ($r^2 = 0.27$) LD with rs7130588, respectively (see **Fig E1, D**). rs6592657, in intron 1 of *LRRC32*, was associated with total serum IgE levels ($P = .00068$) but was not in LD with

the other 3 SNPs. The association with total serum IgE levels was significant and in the same direction for both the combined and separate SARP plus CSGA and TENOR populations (**Table I**), but the association was stronger for the TENOR population compared with the SARP plus CSGA population. To more accurately calculate the variance in our mixed asthma case-control study, these 4 SNPs were tested for association with total serum IgE levels by using stratified weighted regression analysis (see **Table E4** in this article's Online Repository at www.jacionline.org). The results from the stratified weighted analysis were largely comparable with those from standard linear regression analysis (see **Table E2**).

These top 4 SNPs were tested further for association with asthma susceptibility and lung function in the SARP plus CSGA population (661 cases and 363 control subjects). rs6592657 ($P = .04$) and rs7130588 ($P = .06$) were borderline associated with asthma in the SARP plus CSGA cohort (see **Table E5** in this article's Online Repository at www.jacionline.org), whereas rs2508746 and rs10899234 were not. rs6592657 ($P = .02$) was also associated with asthma and in the same direction in TENOR (473 cases and 1892 Illumina control subjects). The association with asthma was most likely related to total serum IgE levels because the association was lost after adjustment for IgE levels in the SARP plus CSGA population (data not shown). No association with lung function (percent predicted FEV₁, percent predicted forced vital capacity [FVC], and FEV₁/FVC ratio) in the SARP plus CSGA population (661 cases and 363 control subjects) and the TENOR population (438 cases) was found for any of these 4 SNPs (see **Table E5**).

A stepwise linear regression approach was used to dissect possible independent associations of the top 4 SNPs with total serum IgE levels. rs2508746 and rs10899234 did not provide more information when added to rs7130588 (based on the likelihood ratio test, data not shown). rs6592657 generated an association signal independent from rs7130588 ($P < .05$ for the likelihood ratio test). Joint analysis was performed on the 2 SNPs (rs7130588 and rs6592657) with independent signals (see **Table E6** and **Fig E2** in this article's Online Repository at www.jacionline.org). The geometric means for total serum IgE levels increased from 52.7 IU/mL (AA) to 80.6 IU/mL (GA) and 81.2 IU/mL (GG) for rs7130588 (risk minor allele G frequency = 0.377; see **Fig E2, A**). rs6592657 (minor allele A frequency = 0.447) was protective, with the geometric means of total serum IgE levels decreasing from 78.2 IU/mL (GG) and 71.9 IU/mL (AG) to 49.1 IU/mL (AA; **Fig E2, B**). After recoding genotypes and counting the number of risk SNPs, the joint effect of rs7130588 and rs6592657 was stronger than the effect of each SNP on its own ($P = 1.14E-08$ and regression slope $\beta = 0.17$; see **Table E6** and **Fig E2, C**). The geometric means of total serum IgE levels increased from 38.7 IU/mL to 58.7 IU/mL and 86.0 IU/mL, with the increase in the number of risk SNPs from 0 (no G for any SNP) to 1 (≥ 1 G in any 1 SNP) and 2 (≥ 1 G in both SNPs).

The total serum IgE level represents a valuable intermediate phenotype for the study of atopic diseases, such as asthma, eczema, and rhinitis. Some genes, such as *FCERIA*, are associated with total serum IgE levels in general but not with specific atopic diseases^{4,5}; other genes, such as *RAD50-IL13*, are

TABLE I. Association results of 10 of 25 SNPs from the *C11orf30-LRRC32* region with total serum IgE levels

No.*	SNP	Coordinate	Gene	Location	Minor allele (MAF)	All†		SARP + CSGA†		TENOR†	
						<i>P</i> value, IgE	β (95% CI)	<i>P</i> value, IgE	β	<i>P</i> value, IgE	β
1	rs4945087	75814130	<i>C11orf30</i>	Flanking 5'	A (0.41)	6.56E-03	−0.08 (−0.13 to −0.02)	.073	−0.062	.048	−0.216
7	rs7130588	75948331		Flanking 3'	G (0.38)	3.40E-05	0.12 (0.06 to 0.18)	.013	0.087	2.75E-04	0.396
8	rs2508746	75948598			T (0.50)	6.77E-04	0.10 (0.04 to 0.15)	.011	0.086	8.47E-03	0.286
9	rs1892953	75950190			G (0.40)	2.47E-03	−0.09 (−0.14 to −0.03)	.018	−0.083	.061	−0.208
11	rs7936562	75955906			T (0.40)	3.72E-03	−0.08 (−0.14 to −0.03)	.023	−0.079	.077	−0.197
13	rs10899234	75966585			A (0.32)	1.11E-03	−0.10 (−0.16 to −0.04)	.041	−0.074	.018	−0.272
21	rs3781701	76047067	<i>LRRC32</i>	3' UTR	T (0.35)	4.57E-03	0.08 (0.03 to 0.14)	.044	0.072	.057	0.210
22	rs1320646	76047695			A (0.25)	.018	−0.08 (−0.14 to −0.01)	.141	−0.059	.126	−0.202
23	rs6592657	76055467		Intron	A (0.45)	6.75E-04	−0.10 (−0.15 to −0.04)	.014	−0.085	.014	−0.261
24	rs10899249	76058005			C (0.49)	.014	0.07 (0.01 to 0.12)	.137	0.052	.020	0.244

E, Scientific notation of the base number 10; MAF, minor allele frequency; UTR, untranslated region.

*The order of SNPs in which 10 of 25 entries are shown when associated with total serum IgE levels ($P < .05$) for combined analysis.

†All includes both SARP plus CSGA and TENOR subjects with total serum IgE levels. SARP + CSGA includes 607 cases and 292 control subjects from the SARP and CSGA populations. TENOR includes 435 cases from the TENOR population.

associated with both total serum IgE levels and atopic diseases^{4,5}; and some genes, such as *HHIP*, are associated with asthma through association with measures of lung function rather than total serum IgE levels.⁶

In this study the *C11orf30-LRRC32* region was strongly associated with total serum IgE levels and weakly associated with asthma susceptibility (Table I and see Table E5). The association between the *C11orf30-LRRC32* region and total serum IgE levels might be specific for non-Hispanic whites. The analysis in a relatively small sample of African Americans (SARP plus CSGA patients with asthma, $n = 324$) did not show any significance ($P = .32$ and $.58$ for rs7130588 and rs6592657, respectively). One shortcoming of this study is that eczema information is unavailable, and thus we cannot exclude the potential confounding effect of atopic dermatitis.

Both *C11orf30* and *LRRC32* are functionally potential candidates for regulation of total serum IgE levels and asthma, and both are expressed in lungs and skin.¹ *C11orf30* encodes the EMSY protein and might play a role in epithelial barrier function.¹ The atopic march hypothesis states that early sensitization through a dysfunctional skin barrier in patients with eczema during infancy can lead to atopic asthma in childhood.⁷ *LRRC32* is a surface biomarker for regulatory T cells and is essential for TGF- β expression and immune tolerance.⁸

Interestingly, on the basis of data from the UCSC genome browser and the ENCODE database, the 4 SNPs (rs7130588, rs2508746, rs10899234, and rs6592657) are located in possible enhancer sites with monomethylation of lysine 4 (H3K4Me1) or acetylation of lysine 27 (H3K27Ac) of the H3 histone protein (see Fig E1, A-C). Therefore 2 independent signals might be involved in the expression regulation of *C11orf30* and *LRRC32*, respectively, and functional studies are necessary to investigate these potential biological mechanisms.

During the preparation of this manuscript, Marenholz et al⁹ reported association of a single SNP, rs7927894, with atopic asthma and hay fever through eczema but not atopy in a large childhood cohort, providing further support for the importance of this 11q13 region.

In summary, there are 2 independent signals, one in *C11orf30* and the other in *LRRC32*, that are strongly associated with total serum IgE levels. The *C11orf30-LRRC32* region might represent a common locus for atopic diseases through

biological pathways involved in the regulation of total serum IgE levels.

Xingnan Li, PhD, MS^a
 Elizabeth J. Ampleford, PhD^a
 Timothy D. Howard, PhD^a
 Wendy C. Moore, MD^a
 Huashi Li, MS^a
 William W. Busse, MD^b
 Mario Castro, MD^c
 Serpil C. Erzurum, MD^d
 Anne M. Fitzpatrick, PhD^e
 Benjamin Gaston, MD^f
 Elliot Israel, MD^g
 Nizar N. Jarjour, MD^h
 W. Gerald Teague, MDⁱ
 Sally E. Wenzel, MDⁱ
 Gregory A. Hawkins, PhD^a
 Eugene R. Bleeker, MD^a
 Deborah A. Meyers, PhD^a

From ^athe Center for Genomics and Personalized Medicine Research, Wake Forest University School of Medicine, Winston-Salem, NC; ^bthe Department of Medicine, University of Wisconsin, Madison, Wis; ^cthe Departments of Medicine and Pediatrics, Washington University School of Medicine, St Louis, Mo; ^dthe Lerner Research Institute, Cleveland, Ohio; ^ethe Department of Pediatrics, Emory University School of Medicine, Atlanta, Ga; ^fthe Department of Pediatrics, University of Virginia Health Systems, Charlottesville, Va; ^gBrigham & Women's Hospital, Harvard University, Boston, Mass; ^hthe Departments of Medicine and Public Health Sciences, University of Wisconsin Hospitals and Clinics, Madison, Wis; and ⁱthe Department of Medicine, University of Pittsburgh, Pittsburgh, Pa. E-mail: xinli@wfubmc.edu.

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METHODS

Study subjects

The SARP non-Hispanic white population was composed of subjects from the NHLBI-funded SARP, and the CSGA population was from the NHLBI CSGA studies. Subjects with mild-to-severe asthma were recruited at SARP centers and carefully characterized, including baseline spirometric results and total serum IgE levels.^{E1,E2} Subjects with asthma who were studied in CSGA by the Wake Forest investigators using a similar protocol were included in the analyses.^{E3} In addition, healthy subjects without asthma recruited by SARP and CSGA investigators were included in the analysis. A positive skin prick test response was defined as a positive response to at least one of 14 common aeroallergens (cockroach, *Dermatophagoides farinae*, diluent, *Alternaria* species, tree mix, *Cladosporium* species, grass mix, *Aspergillus* species, ragweed, cat, histamine, dog, weed mix, and *Dermatophagoides pteronyssinus*) in the SARP study and similarly in the CSGA study.^{E1,E3} Subjects with severe or difficult-to-treat asthma were recruited from the TENOR multicenter study.^{E4,E5} A positive skin prick test response was defined as a positive response to at least 1 allergen (pollen, animals, dust mites, cockroaches, mold, food, and others) for TENOR.^{E4} The SARP, CSGA, and TENOR studies were approved by the appropriate institutional review board at the participating sites, including appropriate informed consent.

Genotyping

DNA was isolated by using standard protocols, and SNP genotyping was performed with the Illumina HumanCNV370 BeadChip (Illumina, Inc, San Diego, Calif) for TENOR. SARP and CSGA samples were genotyped by using the Illumina HumanHap1M BeadChip. Genotyping for both studies was performed with BeadStudio.

Statistical analysis

SARP samples were removed if they (1) had low genotyping call rates (<95%), (2) were discrepant or ambiguous for genetic sex (heterozygous haploid genotype percentage ≥ 0.01 or X-chromosome homozygosity $F \geq 0.9$), (3) were not non-Hispanic whites (as described), (4) failed the check for family relatedness ($PI_HAT > 0.125$), or (5) were detected as an outlier (>6 SDs for the first or second principal component). After subjects meeting these criteria were excluded, SNPs were removed if (1) the call rates were still low (95%), (2) inconsistent with Hardy-Weinberg equilibrium ($P < 10E-04$), and (3) minor allele frequency was less than 0.05. Quality control of the TENOR and CSGA cases was performed in a similar manner.

Twenty-five SNPs (rs4945087, rs4245443, rs7106446, rs1939469, rs1939468, rs2513511, rs7130588, rs2508746, rs1892953, rs1892954, rs7936562, rs6592651, rs10899234, rs4438063, rs7943599, rs10751256, rs947999, rs7931131, rs1941603, rs1892952, rs3781701, rs1320646, rs6592657, rs10899249, and rs947998) in the *C11orf30-LRRC32* region were extracted from GWAS datasets of the SARP, CSGA, and TENOR non-Hispanic white populations and tested for association with total serum IgE levels either as combined (1042 cases and 292 control subjects) or separate for the TENOR (435 cases) and SARP plus CSGA (607 cases and 292 control subjects) populations. The identified top 4 SNPs (rs7130588, rs2508746, rs10899234, and rs6592657) passed Bonferroni correction and were further tested for association with asthma susceptibility, skin prick test response status, and lung function (percent predicted FEV₁, percent predicted FVC, and

FEV₁/FVC ratio) in the SARP plus CSGA population (661 cases and 363 control subjects) and the TENOR population (473 cases and 1892 Illumina common control subjects and 438 cases for asthma and lung function, respectively).^{E5} These 4 SNPs were also tested for association with total serum IgE levels by using stratified weighted regression analysis (svyglm function of survey package in R),^{E6} where the weights were defined as the inverse of variance of total serum IgE levels for asthmatic patients or control subjects, respectively. A linear additive model or logistic additive model was used for analysis of log-transformed total serum IgE levels, percent predicted FEV₁, percent predicted FVC, and FEV₁/FVC ratio or asthma status, respectively, by using PLINK (version 1.06, <http://pngu.mgh.harvard.edu/purcell/plink/>)^{E7} adjusted for age, sex, and significant principal components (EIGENSTRAT, version 3.0, <http://genepath.med.harvard.edu/~reich/Software.htm>).^{E8} A stepwise linear regression in the R program (version 2.5.1, <http://www.r-project.org/>) was used for analysis of independent signals from the top 4 SNPs (rs7130588, rs2508746, rs10899234, and rs6592657) associated with total serum IgE levels. Joint analysis was performed on 2 SNPs (rs7130588 and rs6592657) with independent signals by recoding genotypes with no risk allele or at least 1 risk allele into 0 or 1 and counting the number of risk SNPs.

Haploview (<http://www.broad.mit.edu/mpg/haploview/>) was used to generate LD plots,^{E9} and 95% CIs on D' were used to define blocks.^{E10} The UCSC genome browser (<http://genome.ucsc.edu/>) was used to generate gene structure plot. The ENCODE Consortium data incorporated in the UCSC genome browser was used to present regulatory regions, such as DNase I-hypersensitive clusters, histone methylation, histone acetylation, and transcription factor binding sites.

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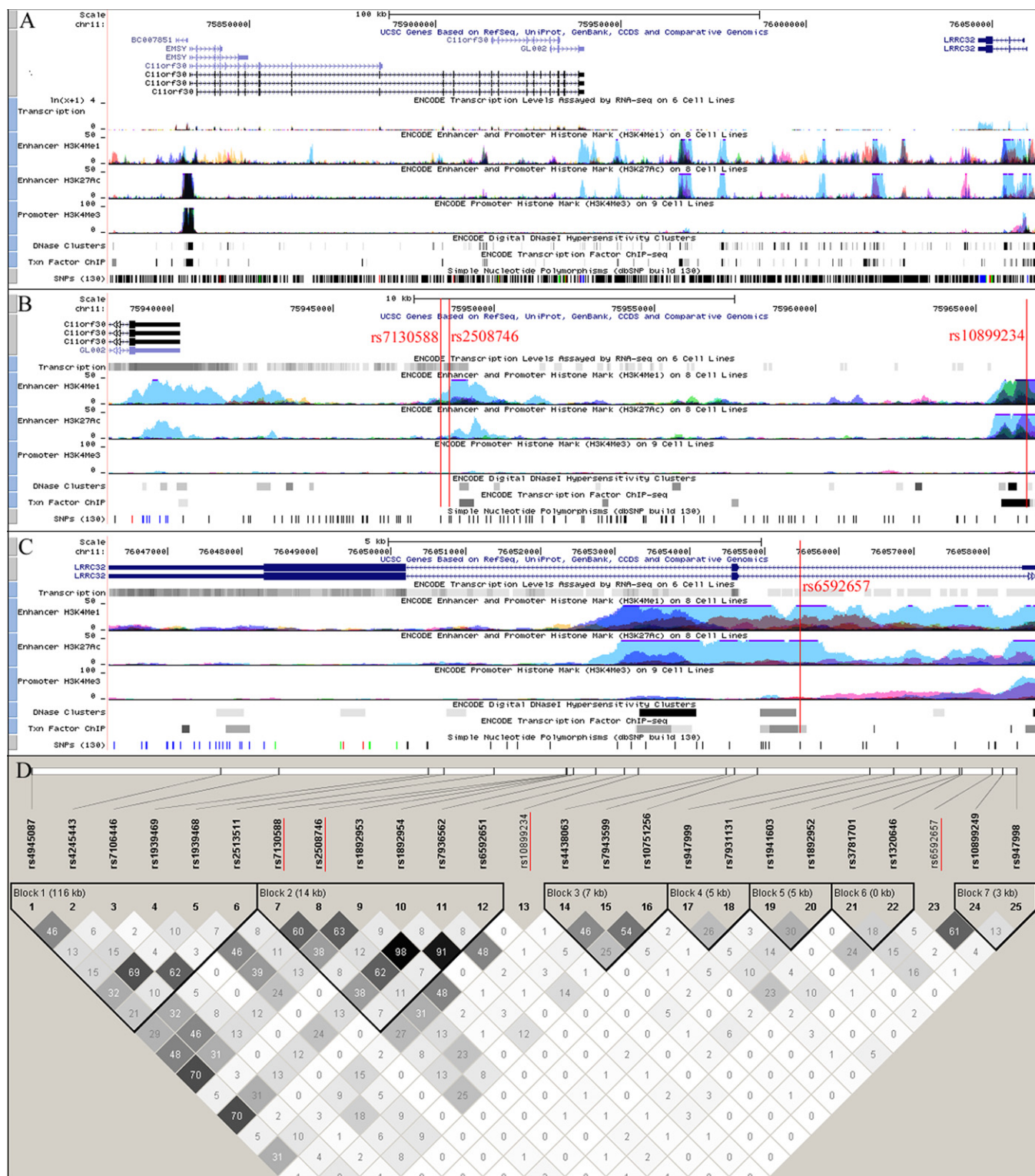


FIG E1. Gene structure and LD plot of the *C11orf30-LRR32* region. **A**, Gene structure of the *C11orf30-LRR32* region. **B**, Gene structure of the 3' end of *C11orf30*. **C**, Gene structure of *LRR32*. **D**, LD plot of 25 SNPs in the *C11orf30-LRR32* region. Fig E1, A through C, were generated by using the UCSC genome browser and ENCODE. Fig E1, D, was generated with Haploview.

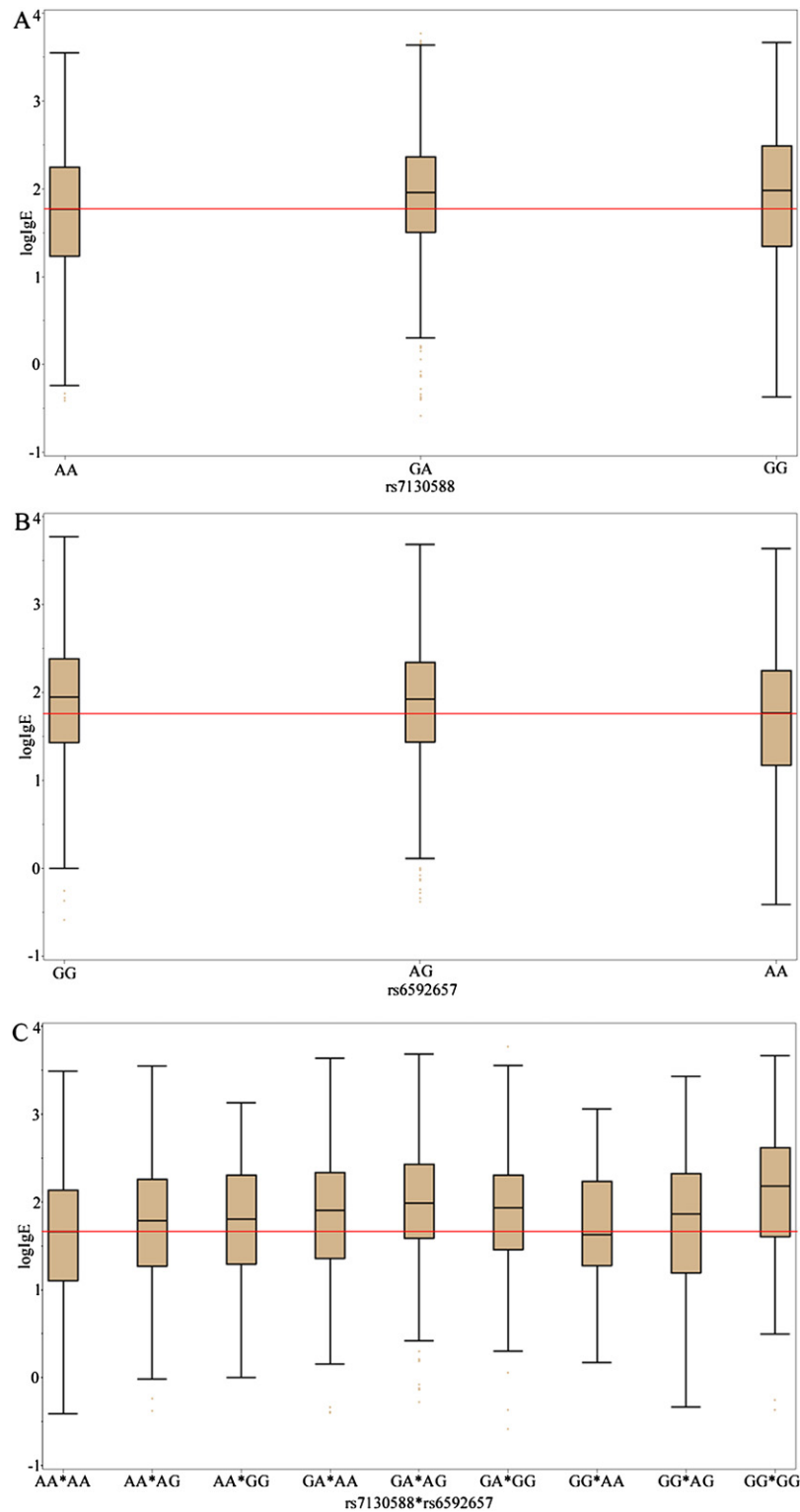


FIG E2. Box plot of rs7130588 and rs6592657 with logIgE levels. **A,** Box plot of rs7130588 with logIgE levels. **B,** Box plot of rs6592657 with logIgE levels. **C,** Box plot of rs7130588 and rs6592657 with logIgE levels.

TABLE E1. Demographics (mean $\pm$ SDs) of non-Hispanic white subjects in the SARP, CSGA, and TENOR studies

	SARP + CSGA		TENOR	<i>P</i> value
	Cases (n = 661)	Control subjects (n = 363)	Cases (n = 438)	
Age (y)	33.1 $\pm$ 15.1	32.1 $\pm$ 10.3	47.0 $\pm$ 18.1	<.0001
Sex (% female)	65	61	63	.53
ppFEV ₁	79.6 $\pm$ 21.0	97.9 $\pm$ 10.7	78.4 $\pm$ 21.0	<.0001
FEV ₁ /FVC	0.74 $\pm$ 0.13	0.82 $\pm$ 0.08	0.72 $\pm$ 0.12	<.0001
Log total serum IgE	2.02 $\pm$ 0.63	1.29 $\pm$ 0.70	1.95 $\pm$ 0.71	<.0001
Geometric mean (IU/mL)	103.9	19.6	88.2	
Skin prick test response (+/–/unknown)	487/103/17	64/87/141	394/15/26	
No.	607	292	435	

ppFEV₁, Percent predicted FEV₁.

TABLE E2. Association results of the top 4 SNPs from the *C11orf30-LRRC32* region with total serum IgE levels with or without asthma status adjusted

SNP	SARP + CSGA				All			
	Unadjusted for asthma status		Adjusted for asthma status		Unadjusted for asthma status		Adjusted for asthma status	
	<i>P</i> value, IgE	β (95% CI)	<i>P</i> value, IgE	β (95% CI)	<i>P</i> value, IgE	β (95% CI)	<i>P</i> value, IgE	β (95% CI)
rs7130588	.013	0.087 (0.018 to 0.16)	.07	0.056 (−0.004 to 0.12)	3.40E-05	0.12 (0.06 to 0.18)	2.12E-04	0.097 (0.046 to 0.15)
rs2508746	.011	0.086 (0.020 to 0.15)	.042	0.061 (0.002 to 0.12)	6.77E-04	0.10 (0.04 to 0.15)	2.01E-03	0.079 (0.029 to 0.13)
rs10899234	.041	−0.074 (−0.15 to −0.003)	.12	−0.050 (−0.11 to 0.013)	1.11E-03	−0.10 (−0.16 to −0.04)	5.65E-03	−0.075 (−0.13 to −0.022)
rs6592657	.014	−0.085 (−0.15 to −0.017)	.15	−0.044 (−0.10 to 0.016)	6.75E-04	−0.10 (−0.15 to −0.04)	1.27E-02	−0.064 (−0.11 to −0.014)

E, Scientific notation of the base number 10.

TABLE E3. Association results of the top 4 SNPs from the *C11orf30-LRRC32* region with skin prick test responses and total serum IgE levels with skin prick test response status adjusted in the SARP and CSGA studies

SNP	Total serum IgE levels adjusted for skin prick test response status		Skin prick tests	
	<i>P</i> value	β (95% CI)	<i>P</i> value	OR (95% CI)
rs7130588	.033	0.069 (0.006 to 0.13)	.080	1.25 (0.97 to 1.59)
rs2508746	.067	0.057 (−0.004 to 0.12)	.097	1.22 (0.96 to 1.54)
rs10899234	.24	−0.039 (−0.10 to 0.026)	.106	0.82 (0.64 to 1.04)
rs6592657	.39	−0.028 (−0.091 to 0.035)	.690	0.95 (0.75 to 1.21)

OR, Odds ratio.

TABLE E4. Association results of the top 4 SNPs from the *C11orf30-LRRC32* region with total serum IgE levels by using stratified weighted analysis

SNP	SARP + CSGA				All			
	Unadjusted for asthma status		Adjusted for asthma status		Unadjusted for asthma status		Adjusted for asthma status	
	<i>P</i> value, IgE	β (95% CI)	<i>P</i> value, IgE	β (95% CI)	<i>P</i> value, IgE	β (95% CI)	<i>P</i> value, IgE	β (95% CI)
rs7130588	.015	0.086 (0.017 to 0.16)	.07	0.058 (−0.005 to 0.12)	4.96E-05	0.12 (0.062 to 0.18)	3.33E-04	0.098 (0.045 to 0.15)
rs2508746	.012	0.086 (0.019 to 0.15)	.043	0.063 (0.002 to 0.12)	8.38E-04	0.096 (0.04 to 0.15)	2.62E-03	0.080 (0.028 to 0.13)
rs10899234	.038	−0.074 (−0.14 to −0.004)	.11	−0.051 (−0.11 to 0.011)	8.51E-04	−0.097 (−0.15 to −0.04)	4.42E-03	−0.076 (−0.13 to −0.024)
rs6592657	.024	−0.079 (−0.15 to −0.011)	.19	−0.041 (−0.10 to 0.020)	1.14E-03	−0.094 (−0.15 to −0.037)	1.72E-02	−0.064 (−0.12 to −0.011)

E, Scientific notation of the base number 10.

TABLE E5. Association results of the top 4 SNPs from the *C11orf30-LRRC32* region with asthma and lung function

SNP	SARP + CSGA*					TENOR†				
	<i>P</i> value, ppFEV ₁	<i>P</i> value, ppFVC	<i>P</i> value, ratio	<i>P</i> value, asthma‡	OR (95% CI)	<i>P</i> value, ppFEV ₁	<i>P</i> value, ppFVC	<i>P</i> value, ratio	<i>P</i> value, asthma‡	OR (95% CI)
rs7130588	.48	.62	.24	.06	1.20 (0.99 to 1.45)	.28	.55	.22	.35	1.12 (0.88 to 1.43)
rs2508746	.96	.37	.40	.14	1.15 (0.95 to 1.37)	.31	.94	.07	.92	1.01 (0.80 to 1.28)
rs10899234	1.00	.30	.20	.21	0.89 (0.73 to 1.07)	.15	.05	.91	.16	0.83 (0.65 to 1.07)
rs6592657	.72	.24	.40	.04	0.82 (0.69 to 0.99)	.80	.29	.38	.02	0.76 (0.61 to 0.96)

OR, Odds ratio; ppFEV₁, percent predicted FEV₁; ppFVC, percent predicted FVC.

*The association between 4 SNPs and asthma or lung function was tested in the SARP plus CSGA population (661 cases and 363 control subjects).

†The association between 4 SNPs and asthma or lung function was tested in TENOR (473 cases and 1892 Illumina control subjects) or TENOR (438 cases).

‡*P* values for association with asthma were generated without adjustment of total serum IgE levels.

TABLE E6. Total serum IgE levels stratified by rs7130588 and rs6592657

rs7130588	GG	GA	AA	<i>P</i> value	β (95% CI)
No. (frequency)	193 (0.145)	619 (0.464)	522 (0.391)		
logIgE (geometric mean [IU/mL])	1.91 $\pm$ 0.79 (81.2)	1.91 $\pm$ 0.71 (80.6)	1.72 $\pm$ 0.73 (52.7)	3.40E-05	0.12 (0.06 to 0.18)
rs6592657	AA	AG	GG		
No. (frequency)	268 (0.201)	656 (0.492)	409 (0.307)		
logIgE (geometric mean [IU/mL])	1.69 $\pm$ 0.80 (49.1)	1.86 $\pm$ 0.72 (71.9)	1.89 $\pm$ 0.71 (78.2)	6.75E-04	−0.10 (−0.15 to −0.04)
No. of risk SNPs	0	1	2		
No. (frequency)	124 (0.093)	541 (0.406)	668 (0.501)		
logIgE (geometric mean [IU/mL])	1.59 $\pm$ 0.82 (38.7)	1.77 $\pm$ 0.72 (58.7)	1.93 $\pm$ 0.72 (86.0)	1.14E-08	0.17 (0.11 to 0.23)

E, Scientific notation of the base number 10.