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C11orf30-LRRC32 region is associated with total serum IgE levels in asthma

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To the Editor

Asthma is a chronic inflammatory respiratory disease characterized by bronchial hyperresponsiveness, increased T_H2 cytokines, and increased serum IgE levels. Atopic dermatitis or eczema is a chronic inflammatory skin disease characterized with epidermal-barrier dysfunction and IgE-mediated sensitization. The only published GWAS of atopic dermatitis identified rs7927894 on chromosome 11q13.5 between chromosome 11 open reading frame 30 (*C11orf30*) and leucine rich repeat containing 32 (*LRRC32*).¹ A replication study further confirmed the association of rs7927894 with childhood eczema.² The same variant is also associated with Crohn's disease, an inflammatory bowel disease.³ Elevated

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total serum IgE levels are common in both asthma and eczema, therefore we studied whether the *C11orf30-LRRC32* region is associated with total serum IgE levels and asthma in three independently ascertained non-Hispanic white populations: the NHLBI funded Severe Asthma Research Program (SARP), the NHLBI Collaborative Studies on the Genetics of Asthma (CSGA) studies, and the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) multi-center study (See additional information on methods in the Online Repository).

After quality control analysis, data from 1,334 subjects (SARP + CSGA with asthma (n = 607), SARP + CSGA healthy controls (n = 292), and TENOR with asthma (n = 435)) were analyzed either combined or separately for association with total serum IgE levels (Table E1). Multiple testing was minimized since analysis was restricted to 25 SNPs covering the whole *C11orf30-LRRC32* region (P value for Bonferroni adjustment was 0.002, P = 0.05/25SNPs).

Four SNPs (rs7130588, rs2508746, rs10899234, and rs6592657) were significantly associated with total serum IgE levels after multiple test adjustment (Table 1 and Figure E1). rs7130588, approximately 8 kb downstream of *C11orf30*, showed the strongest association with total serum IgE levels (P = 0.000034), which remained significant after adjusting for asthma status (P = 0.00021) (Table E2) or skin test positive status (P = 0.033) (Table E3). rs7130588 was marginally associated with skin prick testing status (P = 0.080) (Table E3). rs7130588 is in almost perfect 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 3' of *C11orf30* and were in moderate ($r^2 = 0.60$) and mild LD ($r^2 = 0.27$) with rs7130588, respectively (Figure E1D). rs6592657, in intron 1 of *LRRC32*, was associated with total serum IgE levels (P = 0.00068) but was not in LD with the other three SNPs. The association with total serum IgE levels was significant and in the same direction for both combined and separate SARP + CSGA and TENOR populations (Table 1), but the association was stronger for TENOR compared to the SARP + CSGA population. To more accurately calculate the variance in our mixed asthma case/control study, these four SNPs were tested for association with total serum IgE levels using stratified weighted regression analysis (Table E4). The results from stratified weighted analysis were largely comparable to those from standard linear regression analysis (Table E2).

These top four SNPs were tested further for association with asthma susceptibility and lung function in SARP + CSGA population (661 cases + 363 controls). rs6592657 (P = 0.04) and rs7130588 (P = 0.06) were borderline associated with asthma in SARP + CSGA (Table E5), while rs2508746 and rs10899234 were not. rs6592657 (P = 0.02) was also associated with asthma and in the same direction in TENOR (473 cases + 1892 Illumina controls). The association with asthma was most likely related to total serum IgE levels since the association was lost after adjustment for IgE in SARP + CSGA population (data not shown). No association with lung function (ppFEV₁, ppFVC, and FEV₁/FVC) in the SARP + CSGA (661 cases + 363 controls) and TENOR population (438 cases) was found for any of these four SNPs (Table E5).

A stepwise linear regression approach was used to dissect possible independent association of the top four 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 < 0.05 for the likelihood ratio test). Joint analysis was performed on the two SNPs (rs7130588 and rs6592657) with independent signals (Table E6 and Figure E2). The geometric means for total serum IgE increased from 52.7 (AA) to 80.6 (GA) and 81.2 (GG) for rs7130588 (risk minor allele G frequency = 0.377) (Figure E2A). rs6592657 (minor allele A frequency =

0.447) was protective with the geometric means of total serum IgE decreasing from 78.2 (GG) and 71.9 (AG) to 49.1 (AA) (Figure E2B). Recoding genotypes and counting the number of risk SNPs, the joint effect of rs7130588 and rs6592657 was stronger than each single SNP on its own ($P = 1.14E-08$ and regression slope $\beta = 0.17$) (Table E6 and Figure E2C). The geometric means of total serum IgE increased from 38.7 to 58.7 and 86.0 with the increase in the number of risk SNPs from 0 (no G for any SNP) to 1 (at least one G in any one SNP) and 2 (at least one G in both SNPs).

Total serum IgE levels represent 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 associated with both total serum IgE levels and atopic diseases;^{4, 5} while 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 1 and Table 2). 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 + CSGA with asthma ($n = 324$)) did not show any significance ($P = 0.32$ and 0.58 for rs7130588 and rs6592657, respectively). One shortcoming of this study is that eczema information is unavailable, and thus we can not 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 lung and skin.¹ *C11orf30* encodes the EMSY protein and may play a role in epithelial barrier function.¹ The ‘atopic march’ hypothesis states that early sensitization through dysfunctional skin barrier in eczema during infancy may lead to atopic asthma in childhood.⁷ *LRRC32* is a surface biomarker for regulatory T cells and essential for TGF- β expression and immune tolerance.⁸

Interestingly, based on the UCSC genome browser and ENCODE database, the four SNPs (rs7130588, rs2508746, rs10899234, and rs6592657) are located in possible enhancer sites with mono-methylation of lysine 4 (H3K4Me1) or acetylation of lysine 27 (H3K27Ac) of the H3 histone protein (Figure E1A–1C). Therefore, two 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 preparation of this manuscript, Marenholz et al 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.⁹

In summary, there are two independent signals, one in *C11orf30* and the other in *LRRC32*, strongly associated with total serum IgE levels. The *C11orf30-LRRC32* region may represent a common locus for atopic diseases through biological pathways involved in the regulation of total serum IgE levels.

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Table 1

Association results of 10 of 25 SNPs from the *C11orf30-LRRRC32* region with total serum IgE levels.

No.*	SNP	Coordinate	Gene	Location	Minor Allele (MAF)	AIH [†]		SARP + CSGA [‡]		TENOR [‡]	
						P IgE	BETA (95% CI)	P IgE	BETA	P IgE	BETA
1	rs4945087	75814130		flanking 5'	A (0.41)	6.56E-03	-0.08 (-0.13 -- -0.02)	0.073	-0.062	0.048	-0.216
7	rs7130588	75948331			G (0.38)	3.40E-05	0.12 (0.06 - 0.18)	0.013	0.087	2.75E-04	0.396
8	rs2508746	75948598	<i>C11orf30</i>		T (0.50)	6.77E-04	0.10 (0.04 - 0.15)	0.011	0.086	8.47E-03	0.286
9	rs1892953	75950190		flanking 3'	G (0.40)	2.47E-03	-0.09 (-0.14 -- -0.03)	0.018	-0.083	0.061	-0.208
11	rs7936562	75955906			T (0.40)	3.72E-03	-0.08 (-0.14 -- -0.03)	0.023	-0.079	0.077	-0.197
13	rs10899234	75966585			A (0.32)	1.11E-03	-0.10 (-0.16 -- -0.04)	0.041	-0.074	0.018	-0.272
21	rs3781701	76047067		3' UTR	T (0.35)	4.57E-03	0.08 (0.03 - 0.14)	0.044	0.072	0.057	0.210
22	rs1320646	76047695	<i>LRRRC32</i>		A (0.25)	0.018	-0.08 (-0.14 -- -0.01)	0.141	-0.059	0.126	-0.202
23	rs6592657	76055467		intron	A (0.45)	6.75E-04	-0.10 (-0.15 -- -0.04)	0.014	-0.085	0.014	-0.261
24	rs10899249	76058005			C (0.49)	0.014	0.07 (0.01 - 0.12)	0.137	0.052	0.020	0.244

* The order of SNPs where 10 out of 25 entries are shown when associated with total serum IgE levels ($P < 0.05$) for combined analysis.

[†] All includes both SARP + CSGA and TENOR subjects with total serum IgE levels; SARP + CSGA includes 607 cases and 292 controls from SARP and CSGA populations; TENOR includes 435 cases from TENOR