

Letter to the Editor

***KIF3A* genetic variation is associated with pediatric asthma in the presence of eczema independent of allergic rhinitis**

To the Editor:

Kinesin family member 3A (*KIF3A*) is a susceptibility locus for both asthma¹ and eczema,^{2,3} suggesting that the *KIF3A* associations with asthma may be influenced by eczema comorbidity. However, asthma also has a high rate of allergic rhinitis (AR) comorbidity,⁴ which makes it necessary to weigh the effects of both AR and eczema. Indeed, the lack of data regarding AR was acknowledged as a limitation in a recently published meta-analysis focused on progression from eczema to asthma.⁵ Herein, we elucidated the associations between *KIF3A* single nucleotide polymorphisms (SNPs) and asthma, eczema, and AR, alone and in combination, in the Greater Cincinnati Pediatric Clinic Repository (GCPCR), a well-phenotyped biorepository of more than 7000 children, and controls from the Genomic Control Cohort (GCC), a population-based cohort of 1020 children. Our findings were replicated in the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS), a birth cohort of 762 children with parental atopy. Details of these cohorts have been described previously.^{6,7} Nonallergic controls from the GCC had no family or personal history of asthma and no personal history of any allergic disease. The demographic and clinical characteristics for the GCPCR, GCC, and CCAAPS populations are provided in Table E1 in this article's Online Repository at www.jacionline.org. GCPCR and CCAAPS subjects were genotyped for 19 or 7 tagging SNPs in *KIF3A*, respectively, as described.¹ Tagging SNPs were selected from the CEU (European ancestry) and

YRI (Yoruban ancestry) populations with a coefficient of determination of 0.8 and minor allele frequency of 10% or more in either population using HapMap Genome Browser release #24 (<http://hapmap.ncbi.nlm.nih.gov/>). Twelve of these 19 SNPs were available for the GCC control population. All 12 SNPs were in Hardy-Weinberg equilibrium ($P > .05$) and had minor allele frequencies of more than 10% for GCPCR and GCC separately (see Table E2 in this article's Online Repository at www.jacionline.org). These 12 SNPs remained in the analyses. To assess the gene coverage of these 12 SNPs, we extracted all 42 *KIF3A* SNPs from Hapmap CEU (chr 5:132056221–132101163). Twenty-nine SNPs (not including the 12 tag SNPs) are in linkage disequilibrium (LD) ($r^2 > 0.8$) with at least 1 of our 12 tag SNPs, resulting in a coverage of 96.7% using the following formula⁸ ($G = 10$ million): $((L/(R - T)) \times (G - T) + T)/G$. The location and functionality of these 12 SNPs are presented in Table E2.

Most genome-wide association studies and genetic studies for asthma have not considered comorbid allergic conditions including eczema and AR. We evaluated *KIF3A* associations with asthma in the context of comorbid eczema and/or comorbid AR. Comorbidity was defined as current or past disease. Of the 917 genotyped GCPCR patients for whom the genotyping passed quality control, 577 had asthma, 378 had eczema, and 622 had AR. Among the 577 participants with asthma, 180 also had eczema and 407 had AR (see Fig E1 in this article's Online Repository at www.jacionline.org). The following case groups were used: all asthma, asthma + eczema, asthma without eczema, pure eczema, asthma + AR, asthma without AR, and pure AR. Analyses were performed using GCPCR cases and GCC nonallergic control participants. We restricted the analyses to the white population because of a limited number of black

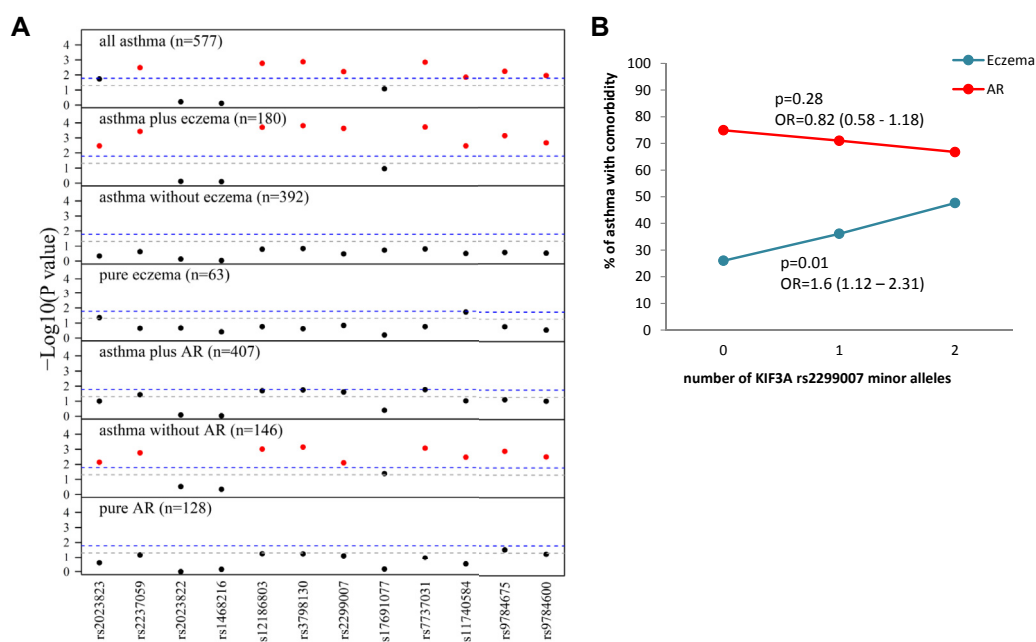


FIG 1. A, Associations between tagging *KIF3A* SNPs and allergic phenotypes compared with nonallergic controls. Gray dotted lines: Significance at $P = .05$. Blue dotted lines: Significance after Bonferroni correction. **B,** Percentage of all children with asthma in the GCPCR cohort who also had comorbid eczema (red line) or AR (blue line), as a function of the number of *KIF3A* rs2299007 minor alleles. OR, Odds ratio.

TABLE I. Genetic associations of SNPs in *KIF3A* with the asthma + eczema and asthma without eczema phenotypes in discovery GCPCR/GCC and validation in the CCAAPS population

<i>KIF3A</i> SNP	<i>R</i> ² *	GCPCR/GCC†								CCAAPS‡					
		Asthma + eczema (N = 180)				Asthma without eczema (N = 392)				Asthma + eczema (N = 29)			Asthma without eczema (N = 25)		
		OR	95% CI	<i>P</i> value§	<i>P</i> value	OR	95% CI	<i>P</i> value§	<i>P</i> value	OR	95% CI	<i>P</i> value§	OR	95% CI	<i>P</i> value§
rs2023823	0.47	1.51	1.15-1.99	.003	.44	1.1	0.85-1.43	.46	.81						
rs2237059	0.94	1.84	1.32-2.57	.0004	.50	1.23	0.88-1.73	.23	.44						
rs2023822	0.03	1.06	0.73-1.53	.76	.37	1.06	0.76-1.47	.73	.57						
rs1468216	0.03	1.05	0.73-1.52	.78	.37	1.02	0.73-1.42	.91	.75						
rs12186803	1	1.90	1.35-2.66	.0002	.33	1.28	0.91-1.80	.16	.08	2.67	1.02-7.23	.047	1.22	0.34-3.9	.75
rs3798130	1	1.92	1.37-2.68	.0002	.18	1.29	0.92-1.82	.15	.03	2.4	0.93-6.35	.07	1.08	0.31-3.4	.9
rs2299011	1									2.4	0.93-6.35	.07	1.08	0.31-3.4	.9
rs2299007	NA	1.89	1.35-2.66	.0002	NA	1.19	0.84-1.69	.33	NA						
rs17691077	0.03	0.71	0.47-1.08	.11	.26	0.79	0.55-1.12	.19	.24						
rs12514685	1									2.36	0.92-6.23	.076	1.05	0.3-3.33	.93
rs7737031	1	1.9	1.36-2.65	.0002	.41	1.28	0.81-1.81	.16	.06	2.62	1.01-7.1	.051	1.19	0.33-3.82	.78
rs11740584	0.48	1.51	1.15-1.99	.003	.39	1.15	0.88-1.49	.31	.57						
rs1080001	1									2.67	1.02-7.23	.047	1.22	0.34-3.9	.75
rs9784675	0.89	1.77	1.27-2.47	.001	.92	1.21	0.86-1.70	.27	.48	2.61	1-7.09	.052	1.2	0.34-3.84	.77
rs9784600	0.89	1.68	1.21-2.35	.002	.26	1.2	0.85-1.68	.3	.71						

OR, Odds ratio.

**R*² values relative to rs2299007 were calculated using Hapmap CEU data.

†Nonallergic children from the GCC without a family or personal history of asthma served as controls for the GCPCR discovery cohort.

‡Children without allergic disease or skin prick testing positivity served as controls. *P* values < .05 were considered statistically significant and are shown in boldface.§*P* values were obtained from the Wald statistic.||*P* values were obtained from conditional analysis with SNP rs2299007 included as covariate.

participants. Assuming an additive genetic model, logistic regression was used to obtain odds ratios and *P* values for associations between each SNP and the respective allergic phenotypes (see Table E3 in this article's Online Repository at www.jacionline.org). The analyses were adjusted for age and sex. To correct for multiple testing, we determined the average pairwise LD (measured by *r*² statistic) for all SNP combinations and calculated the Bonferroni correction (<http://www.quantitativeskills.com/sisa/>).

P values were obtained from the Wald statistic. When all patients with asthma were compared with the nonallergic controls, 9 of the 12 *KIF3A* SNPs were significantly associated with asthma (Fig 1, A) as we previously published.¹ When the case group was restricted to asthma + eczema, the significance of the association increased for all SNPs examined, even though the sample size decreased (Fig 1, A, and Table I). There was no association of *KIF3A* with the asthma without eczema group (Fig 1, A, and Table I).

We next evaluated the impact of AR. If the association of *KIF3A* with asthma + eczema was driven primarily by underlying AR, then the association of *KIF3A* with asthma + AR should be similar to asthma + eczema. However, none of the *KIF3A* SNPs was associated with asthma + AR (Fig 1, A). Thus, the increased association of *KIF3A* with asthma in the presence of comorbidity is specific for asthma + eczema.

In addition, we performed analyses using "pure" phenotypes (eg, eczema without asthma or AR and AR without asthma or eczema). Many of the GCPCR children with an eczema-only diagnosis were still of preschool age at the time of data collection, and thus unlikely to have developed asthma. Therefore, the pure eczema group was limited to children for whom we had follow-up until at least age 7 years. Again, there was no association of *KIF3A* SNPs with pure eczema or pure AR, supporting that *KIF3A* is associated specifically with eczematous children who progress to develop asthma (Fig 1, A).

Although the SNPs genotyped herein were identified by HapMap release #24 as tagging SNPs, we found considerable LD in the region spanning *KIF3A* (see Fig E2 in this article's Online Repository at www.jacionline.org). To evaluate the number of independent signals in the *KIF3A* region, we performed conditional analyses with rs2299007, one of the SNPs most strongly associated with asthma + eczema, as a covariate. The results gave no indication of multiple signals (Table I). Consequently, subsequent analyses were focused on rs2299007.

To further explore the specificity of eczema comorbidity among patients with asthma, we applied logistic regression model to examine the association between asthma + eczema comorbidity and *KIF3A*. Sex and age were included as covariates in the model. We applied the same model to asthma + AR comorbidity. There was a significant relationship between rs2299007 and asthma + eczema (Fig 1, B), with an odds ratio of 1.6 for each additional minor allele (*P* = .01). The asthma + AR phenotype did not exhibit any association with *KIF3A* rs2299007 (*P* = .28).

We next replicated our findings in an independent birth cohort, CCAAPS, using the additive logistic regression model in the white population.⁷ Children without allergic disease or skin prick testing positivity served as controls (N = 59). *P* values and odds ratios were obtained after adjusting for sex. Two of the 7 genotyped *KIF3A* SNPs were significantly associated with the asthma + eczema phenotype, including 1 SNP, rs12186803, that was also significantly associated with asthma + eczema in GCPCR (Table I). Using the strictest definition of genetic replication provided by Sullivan,⁹ we observed SNP level validation for rs12186803. In contrast, none of the SNPs was associated with asthma without eczema (*P* > .7). Although none of the SNPs was significant in CCAAPS after multiple testing correction, most likely because of the small sample size, all the

KIF3A SNPs in the CCAAPS cohort had odds ratios of more than 2.3 for associations with asthma + eczema, which is greater than the odds ratios found in the discovery cohort.

A limitation of our study is the relatively small sample size of the subgroup with eczema only, which may in part account for the lack of association between *KIF3A* and pure eczema. Our results reveal that the association with asthma is evident only in the asthma + eczema group and is not seen in the asthma without eczema group. These data support a recent study that reported that the *IL4/KIF3A* locus is associated with asthma/eczema comorbidity.⁸

Although previous studies have demonstrated *KIF3A* genetic associations with asthma¹ or eczema,^{2,3} these previous studies did not characterize allergic comorbidities. Similarly, the study by Marenholz et al⁵ did not examine the potential role of AR. In our study, we demonstrate that the association of *KIF3A* is with asthma + eczema. The presence of AR comorbidity did not increase the genetic association of *KIF3A* with asthma or even with asthma + eczema. Thus, our results indicate that asthma + eczema constitutes a distinct asthmatic phenotype characterized by an association with *KIF3A* SNPs, which is not strengthened by AR. The specific association of *KIF3A* with asthma + eczema may have important clinical consequences.

We acknowledge the administrative assistance of Cynthia Chappell. We thank the children and families who participated in this study.

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Disclosure of potential conflict of interest: E. Johansson's institute has received a grant and support for travel from the National Institutes of Health (NIH) for this work. J. M. B. Myers' institute has received a grant and support for travel from the NIH for this work and has received grants from NIH for other works. L. J. Martin's institution has received a grant from the NIH for this work and grants from the American Heart Association for this work and for Methods for Assessing Responsiveness to Asthma Treatment Based on VNN-1 Expression and Promoter Methylation (Patent # US2015/030984). H. He has received a grant from the NIH for this work. T. Mersha's institution has received an NIH grant (no. R01HL132344) for other works. P. Ryan's institute has received a grant from the NIEHS (National Institute of Environmental Health Sciences) for this work. G. K. LeMasters' institute has received a grant from the NIH for this work, grants from the NIH and Industry Refractory Ceramic Fibers for other work, and a government patent for her work. D. I. Bernstein's institution has received a grant from the University of Cincinnati for this work and grants from GlaxoSmithKlein, Merck, Novartis, Genentech, AstraZeneca, Pearl, and Circassia Pharmaceuticals for other work; has personally received board membership from ABAI (The American Board of Allergy and Immunology) National Task Force PP; consultancy fees from TEVA and Merck; payment for lectures from Merck and AZ; and payment for the development of educational presentations from SANOFI. J. Lockey's institute has received a grant from the NIH (grant no. R01 ES011170-08) for this work. G. K. K. Hershey's institute has received a grant from the NIH for this work and a grant from Adare Pharmaceuticals, Inc. for other work. The rest of the authors declare that they have no relevant conflicts of interest.

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<http://dx.doi.org/10.1016/j.jaci.2017.02.003>

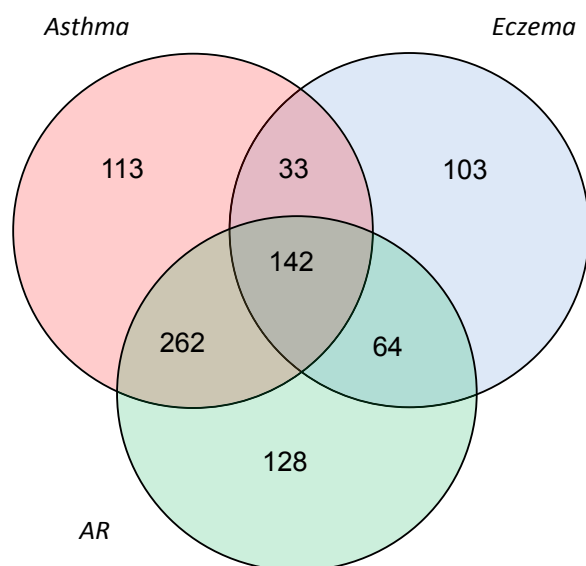


FIG E1. Venn diagram showing composite phenotypes in the GCPCR cohort and sample sizes for each phenotype. Because some children in the GCPCR cohort lacked a definitive diagnosis for 1 or 2 diseases, they could not be placed in the Venn diagram. Therefore, the total number is slightly lower than that indicated in [Table E1](#).

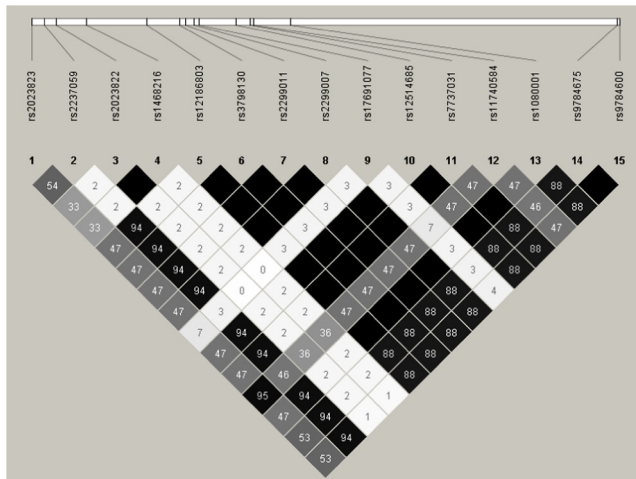


FIG E2. R^2 plot of LD between KIF3A SNPs used in the genotyping of GCPCR and CCAAPS. R^2 values were calculated for the HapMap CEU population.

TABLE E1. Demographic and clinical characteristics of the 3 cohorts used in the study

Characteristic	Discovery		Replication
	GCPCR	GCC*	CCAAPS†
N	917	412	392
Age (y), mean $\pm$ SD	7.95 $\pm$ 4.91	10.86 $\pm$ 4.29	NA
Sex: male (%)	58.2	47.6	54.8
Asthma (%)	62.9	0	13.8
Eczema (%)	41.2	0	37.0
AR (%)	67.8	0	19.6
Nonallergic controls (%)	0	100	15.1

SPT, Skin prick testing.

*Nonallergic controls from the GCC did not have any family or personal history of asthma and no personal history of any allergic disease.

†In the CCAAPS, children without allergic disease or SPT positivity were defined as nonallergic controls.

TABLE E2. Annotation of KIF3A SNPs used in the discovery cohort

SNP	Position on chromosome 5*	MAF (Asthma)	MAF (GCC)	HWE† (Asthma)	HWE† (GCC)	Functionality	CpG-SNP
rs9784600	132734155	0.3024	0.2633	0.8432	0.4457	Intronic	
rs9784675	132734047	0.171	0.1229	0.7684	0.8181	Intronic	
rs11740584	132711097	0.1398	0.1396	0.862	0.6811	Intronic	X
rs7737031	132710898	0.136	0.1396	0.7224	0.6811	Intronic	
rs17691077	132707659	0.1658	0.1165	0.651	0.4726	Intronic	
rs2299007	132707340	0.1649	0.1165	0.6497	0.4726	Intronic	X
rs3798130	132706454	0.1571	0.1153	1	0.4657	Intronic, missense	
rs12186803	132704377	0.1049	0.1286	0.822	1	Intronic	
rs1468216	132700560	0.1652	0.1165	0.6501	0.4726	Intronic	X
rs2023822	132698654	0.299	0.2573	1	0.6079	Intronic	
rs2237059	132697920	0.1675	0.1238	0.552	0.6553	Intronic	
rs2023823	132697114	0.1649	0.125	0.6497	0.8208	Intronic	X

MAF, Minor allele frequency.

*Genome Reference Consortium GRCh38.p2 primary assembly.

†P values for Harvey-Weinberg equilibrium.

TABLE E3. Associations between *KIF3A* SNPs and asthma phenotypes in GCPCR

KIF3A SNP	All asthma (n = 577)		Asthma + eczema (n = 180)		Asthma without eczema (n = 392)		Pure eczema (n = 63)		Asthma + AR (n = 407)		Asthma without AR (n = 146)		Pure AR (n = 128)	
	OR	P value	OR	P value	OR	P value	OR	P value	OR	P value	OR	P value	OR	P value
rs2023823	1.30	.02	1.51	.003	1.10	.46	1.52	.044	1.23	.10	1.55	.007	1.21	.26
rs2237059	1.53	.003	1.84	.0004	1.23	.23	1.40	.23	1.39	.04	1.87	.002	1.47	.07
rs2023822	1.08	.61	1.06	.76	1.06	.73	1.36	.22	1.04	.82	1.23	.30	1.00	1.00
rs1468216	1.05	.76	1.05	.78	1.02	.91	1.25	.39	1.02	.92	1.16	.45	0.92	.70
rs12186803	1.58	.002	1.90	.0002	1.28	.16	1.44	.18	1.45	.02	1.94	.001	1.51	.06
rs3798130	1.59	.001	1.92	.0002	1.29	.15	1.38	.24	1.46	.02	1.97	.0007	1.50	.06
rs2299007	1.50	.006	1.89	.0002	1.19	.33	1.48	.15	1.44	.02	1.72	.008	1.46	.08
rs17691077	0.76	.08	0.71	.11	0.79	.19	0.86	.62	0.87	.40	0.61	.04	1.10	.67
rs7737031	1.59	.001	1.90	.0002	1.28	.16	1.44	.18	1.46	.02	1.95	.0008	1.41	.11
rs11740584	1.32	.01	1.51	.003	1.15	.31	1.63	.019	1.23	.10	1.61	.003	1.19	.30
rs9784675	1.48	.006	1.77	.0007	1.21	.27	1.46	.16	1.32	.07	1.90	.001	1.57	.03
rs9784600	1.44	.01	1.68	.002	1.20	.30	1.36	.26	1.30	.09	1.81	.003	1.49	.06

Nonallergic controls from the GCC served as controls (n = 412). P value was obtained by Wald test. $P < .0166$ was considered statistically significant.

OR, Odds ratio.