

Letter to the Editor

Associations between the 17q21 region and allergic rhinitis in 5 birth cohorts

To the Editor:

The high heritability and comorbidity between allergic rhinitis and asthma suggest common etiologies and genetic susceptibility loci. Among the most robust signals for asthma is the chromosomal locus 17q21.¹ Studies that examined whether this strong asthma locus is also associated with allergic rhinitis have yielded conflicting results. A recent large genome-wide association study (GWAS)² and a candidate gene study³ identified associations between genetic variants at the 17q21 locus and allergic rhinitis, in contrast to null findings in previous GWASs on allergic rhinitis^{4,5} and self-reported allergy.⁶ Large, well-defined studies are needed to clarify these inconsistencies.

We pooled data from 5 birth cohorts not included in the aforementioned GWASs (Children, Allergy, Milieu, Stockholm, Epidemiological Survey [BAMSE], Canadian Asthma Primary Prevention Study [CAPPS], German Infant study on the influence of Nutritional Intervention plus environmental and genetic influences on allergy development [GINIplus]/Lifestyle-related factors, Immune System and the development of Allergies in East and West Germany plus the influence of traffic emissions and genetics study [LISAPlus], Prevention and Incidence of Asthma and Mite Allergy [PIAMA], and Study of Asthma Genes and the Environment [SAGE]; $N_{\text{total}} = 4624$ children, 92.7% white) and examined whether 7 single nucleotide polymorphisms (SNPs) at the 17q21 locus are associated with allergic rhinitis from early childhood to adolescence, and the effects of comorbidity with asthma on the associations.

Allergic rhinitis was defined as concomitantly reported rhinitis and positive sensitization to any aeroallergen (age range 4-16 years in pooled data). Seven SNPs, including top GWAS hits for asthma (rs7216389 and rs2305480),¹ were extracted from genotyped (BAMSE) or imputed genome-wide (other cohorts) data and coded as 0, 1, and 2 according to the number of effect alleles. Cohort-specific study designs, outcome definitions, and genotyping/imputation are provided in this article's [Methods section](#) and [Table E1](#) in the Online Repository at www.jacionline.org. The effect of each SNP on allergic rhinitis over time was analyzed using generalized estimating equation models (logit link and exchangeable correlation structure) adjusted for age and cohort (pooled models only). Associations were calculated per cohort and in the combined pooled data. Odds ratios with corresponding 95% CIs are presented.

Allergic rhinitis was reported at least once by 969 of the 4624 children ([Table I](#)). The proportion of cases generally increased with age (see [Table E2](#) in this article's [Online Repository](#) at www.jacionline.org). Effect allele frequencies were very similar across cohorts for all SNPs (see [Table E3](#) in this article's [Online Repository](#) at www.jacionline.org). The correlation between 5 of the SNPs (rs2305480, rs7216389, rs4065275, rs8076131, and rs12603332) was high ($r^2 > 0.7$, $D' > 0.9$) and more moderate

between these 5 SNPs and the other 2 ($r^2 < 0.3$, $D' > 0.9$; rs17608925 and rs3744246).

Allergic rhinitis and 6 of the 7 studied SNPs were significantly associated in the pooled data ([Table I](#)). Because the SNPs are in high linkage disequilibrium, the associations are not independent. Cohort-specific risk estimates were consistent across all cohorts except the smallest cohort CAPPS (see [Table E4](#) in this article's [Online Repository](#) at www.jacionline.org). Associations stratified by sex were significant only among males, although the direction of effects was similar in males and females (data not shown).

Sensitivity analyses were conducted to assess whether associations with allergic rhinitis were modified by the copresence of asthma. Associations between the 17q21 variants and allergic rhinitis with concomitant asthma appeared more pronounced (although not significantly) than when allergic rhinitis or asthma was modeled independently ([Table I](#)). Risk estimates for allergic rhinitis without concomitant asthma appeared smaller but were also significant/borderline significant for 5 SNPs in high linkage disequilibrium. Associations with allergic rhinitis were similar after adjustment for asthma during early life (3-8 years). However, stratified analyses indicated that associations between the SNPs and allergic rhinitis were significant only among those with a history of asthma ([Fig 1](#)).

In our study, risk estimates for the 17q21 locus with concomitant allergic rhinitis and asthma appeared largest, which is intuitive given that significant associations were observed for asthma and allergic rhinitis modeled independently. These results have been observed by others² and may suggest that the 17q21 locus is involved in the development of multiple clinical manifestations or a more severe type of disease, possibly via a causal pathway involving asthma. An asthma-dependent mechanism is supported by the stratified analyses in which associations between the SNPs and allergic rhinitis were most pronounced for those with a history of asthma. Furthermore, the 17q21 locus appears to be a stronger risk factor for asthma than for allergic rhinitis.² Nevertheless, because weaker borderline significant longitudinal associations for allergic rhinitis without concomitant asthma were also observed, we are unable to exclude the possibility that any effect of 17q21 variation on allergic rhinitis may also be mediated through an asthma-independent pathway, as has been suggested by others.³ However, the null associations with allergic rhinitis for those without any history of asthma observed in this study do not support this hypothesis ([Fig 1](#)).

Allele-specific differences in gene expression at 17q21 are being investigated.^{7,8} However, how these genes (and other genetic, epigenetic, and gene-environment influences) may affect asthma or allergic rhinitis development remains under study. A functional role for ORM1-like protein 3 in regulating eosinophil trafficking, recruitment, and degranulation via the regulation of integrins and CD48 was recently identified.⁹ Because eosinophils are involved in immune and inflammatory responses to allergens, this may represent a possible mechanism by which 17q21 variation affects allergic asthma and allergic rhinitis.

Our study results are based on a substantially larger sample size and longer follow-up than any previous candidate-gene study for allergic rhinitis studying this region. It is noteworthy that the

TABLE I. Pooled longitudinal associations between 7 SNPs at the 17q21 locus and health outcomes*

SNP	Gene	Effect allele	EAF	Allergic rhinitis† (case ever = 969 of 4624)		Asthma‡ (case ever = 571 of 4619)		Allergic rhinitis with concomitant asthma§ (case ever = 234 of 4019)		Allergic rhinitis without concomitant asthma§ (case ever = 816 of 4425)	
				N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
rs2305480	<i>GSDMB</i>	A	0.45	4605	0.85 (0.77-0.94)	4600	0.83 (0.72-0.96)	4002	0.72 (0.59-0.88)	4407	0.89 (0.80-0.99)
rs7216389	<i>GSDMB</i>	T	0.49	4604	1.15 (1.04-1.27)	4599	1.15 (1.01-1.32)	4001	1.35 (1.12-1.63)	4408	1.10 (0.99-1.22)
rs4065275	<i>ORMDL3</i>	G	0.50	4421	1.14 (1.03-1.26)	4417	1.13 (0.98-1.29)	3859	1.35 (1.11-1.64)	4266	1.09 (0.98-1.22)
rs8076131	<i>ORMDL3</i>	G	0.45	4417	0.86 (0.77-0.95)	4413	0.85 (0.73-0.98)	3856	0.73 (0.60-0.89)	4262	0.89 (0.80-1.00)
rs12603332	<i>ORMDL3</i>	C	0.50	4618	1.15 (1.04-1.27)	4426	1.13 (0.98-1.29)	4014	1.34 (1.11-1.61)	4420	1.10 (0.99-1.23)
rs17608925	<i>ORMDL3</i>	C	0.11	4414	0.88 (0.74-1.05)	4410	0.99 (0.79-1.25)	3853	0.94 (0.67-1.32)	4259	0.89 (0.74-1.07)
rs3744246	<i>ORMDL3</i>	T	0.20	4607	0.86 (0.75-0.97)	4602	0.89 (0.75-1.06)	4004	0.83 (0.65-1.06)	4411	0.89 (0.77-1.02)

Case ever, Whether a child ever had a positive report at any follow-up; EAF, effect allele frequency; *GSDMB*, gasdermin B; N, number of children included in the model; OR, odds ratio; *ORMDL3*, ORM1-like protein 3.

*Models were adjusted for age and cohort.

†Age-specific controls were defined as those without allergic rhinitis. P values of significant pooled associations ranged from .002 for rs2305480 to .017 for rs3744246. Bonferroni-corrected P value corresponds to $.05/7 = .007$. The associated SNPs are in linkage disequilibrium ($r^2 > 0.2$, $D' > 0.9$).

‡Age-specific controls were defined as those without asthma.

§Age-specific controls were defined as those without allergic rhinitis or asthma.

||P < .05.

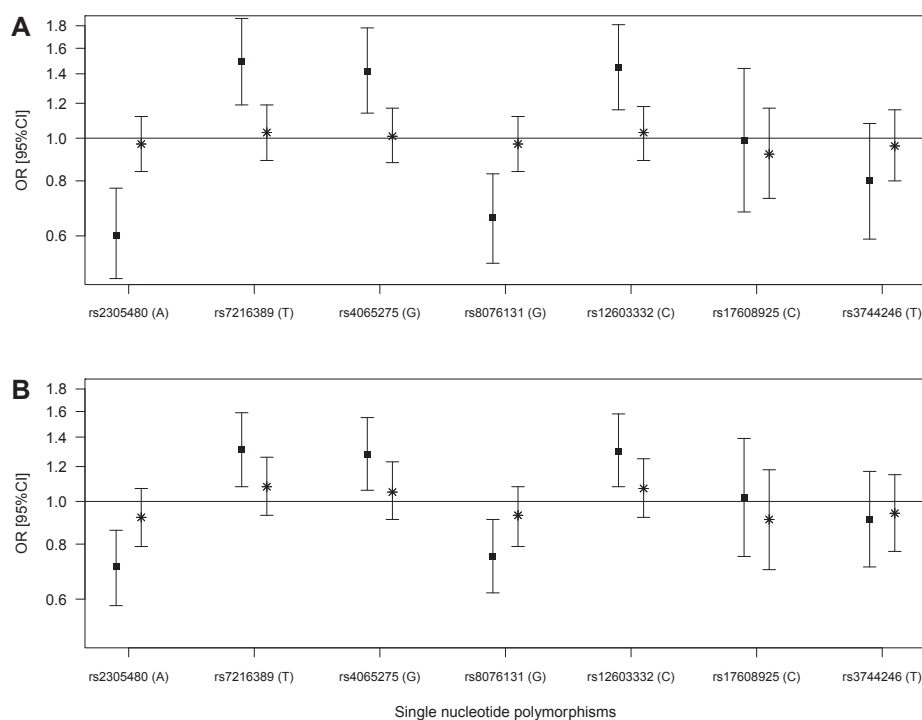


FIG 1. Pooled longitudinal associations between the 17q21 SNPs and allergic rhinitis, stratified by early-life (3-8 years) (A) and ever (B) asthma (black squares = yes; stars = no). Models were adjusted for age and cohort and only included cohorts with data on early-life asthma (BAMSE, GINI/LISA, and PIAMA). Controls were defined as children with no allergic rhinitis or asthma.

cohort-specific analyses, although consistent in trend, did not independently reach statistical significance in almost all cases. This highlights the need to carefully pool or meta-analyze homogenous data to achieve sufficient statistical power. It nevertheless remains possible that our study may have had less power to detect associations that were found to be without or with borderline significance. The SNPs studied were limited to those available for the largest subset of the cohorts, which included top hits from previous asthma GWASs.¹ It is reassuring that we observed significant associations for 6 of the 7 SNPs (which were in high linkage disequilibrium) and that associations

were consistent across cohorts despite slightly different outcome definitions (doctor diagnoses [CAPPs, GINI/LISA, and SAGE], rhinitis symptom reports [PIAMA], or both [BAMSE]). This consistency also argues against the interpretation that the results are due to chance. Furthermore, associations between allergic rhinitis and the 17q21 locus would have remained significant after a very conservative Bonferroni correction (Table I).

In summary, genetic variants at the 17q21 locus were significantly associated with allergic rhinitis, primarily with concomitant asthma, in a pooled longitudinal analysis of 5 birth

cohorts. These results support the hypothesis of a shared genetic susceptibility between asthma and allergic rhinitis.

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METHODS

Outcome definitions

The cohort-specific rhinitis and asthma definitions, aeroallergens tested, and frequencies of follow-up are provided in Table E1. Parent-completed questionnaires were used to collect data on rhinitis and asthma. Aeroallergen sensitization was assessed as any specific IgE level of 0.35 kU/L or more for BASME, GINI/LISA, and PIAMA. For CAPPs and SAGE, sensitization was assessed by using skin prick testing. A positive reaction was defined as having a wheal diameter of 3 mm or more. Although not all cohorts had information on all aeroallergens, several aeroallergens were tested in each cohort (Table E1). Each cohort received ethical approval from its local authorized institutional review board. Statistical analyses were conducted in R, version 2.13.1 (www.r-project.org).

Genetic analyses

The 7 SNPs examined in this study were in Hardy-Weinberg equilibrium ($P > .01$). For BAMSE, these SNPs were genotyped in a subset of the cohort ($N = 2033$ with DNA extracted from blood samples available) by Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (SEQUENOM, Inc, San Diego, Calif). For the CAPPs, GINI/LISA, PIAMA, and SAGE cohorts, information on these 7 SNPs was extracted from imputed genome-wide data. All imputed allele dosage data were recoded to hard coding (0, 1, and 2) before further analysis. As a sensitivity analysis, the longitudinal model results for the GINI/LISA cohort were compared using hard and allele dosage coding for the SNPs and the results were very consistent.

For GINI/LISA, DNA samples from 1027 children and 69 children were analyzed using the Affymetrix Human SNP Arrays 5.0 and 6.0, respectively. Genotypes were called using the BRLMM-P (Affymetrix 5.0) or BIRDSEED V2 algorithm (Affymetrix 6.0). The genotype data were subjected to quality control filters on the variant and individual levels. Variants were excluded on the basis of the following criteria: a call rate below 95%, a minor allele frequency below 1%, or a Hardy-Weinberg equilibrium P value below 1×10^{-5} (~18% excluded). Only those individuals who had a call rate above 95%, a heterozygosity value within ± 4 SDs of the mean, and who passed a sex check and the similarity quality control step based on multidimensional scaling plots were retained for subsequent imputation. The genotype data were prephased using SHAPEIT v2^{E1,E2} and imputed using IMPUTE v2^{E3} against reference haplotypes from the 1000 Genomes Project (Phase I integrated variant set [v3; includes individuals from all ancestries]; March 2012, updated August 26, 2012; limited to variants with more than 1 minor allele copy). All 7 SNPs used for the present analysis were imputed with good imputation quality (IMPUTE v2 INFO > 0.94).

For PIAMA, DNA was extracted from blood or buccal swabs. DNA of 1377 children was genotyped on the Illumina Omni Express Exome Chip and DNA of 288 children was genotyped with the Omni Express chip, both at the Genomics Facility of the University Medical Center Groningen. DNA of 404 children was genotyped at the Centre National de Genotypage (CNG, Evry, France) as part of the GABRIEL consortium.^{E4} SNPs were harmonized by base-pair position annotated to genome build 37, name, and annotation of strand for each platform. Discordant or duplicate SNPs or SNPs that showed large differences in allele frequencies (>15%) were removed. After quality

control, a total of 1968 individuals remained and imputation was performed per platform using IMPUTE 2.0 against the reference data set of the CEU panel of the 1000 Genomes project (version March 2012). SNPs of high quality (info-score IMPUTE ≥ 0.7) were merged into 1 data set using GTOOL and used for further analysis.

For CAPPs and SAGE, data on only 4 SNPs (rs2305480, rs7216389, rs12603332, and rs3744246) were available. In total, 956 samples from parents and children were genotyped using the Illumina HumanHap550 SNP Array. Genotypes were subjected to the following quality control filters for variants and individual samples. Variants were excluded on the basis of the following criteria: a call rate below 95%, a minor allele frequency below 1%, failure of Hardy-Weinberg equilibrium P value below 1×10^{-4} , and SNPs with more than 2 Mendelian errors. Individual samples were retained if they had a call rate of more than 97% and a heterozygosity value within ± 3 SDs of the mean, and samples additionally had to pass gender and Mendelian transmission error checks. Multidimensional scaling was used to check for population stratification and to identify monozygotic twins ($n = 2$) and duplicate samples. Imputation was performed using MaCH^{E5} and HapMap2 r22 reference population. SNPs needed to be imputed with an $r^2 \geq 0.99$ to be used in the analysis.

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TABLE E1. Characteristics of participating cohorts

Cohort (country)	Full name of cohort	Study type	Recruitment	Sample size*	Ages (y) available †	Rhinitis definition	Asthma definition	Aeroallergens tested
BAMSE (Sweden)	Children, Allergy, Milieu, Stockholm, Epidemiological Survey ^{E6}	Population-based birth cohort with wheeze nested case-control	1994-1996	1953	4, 8, 16	Symptoms (sneezing, runny or blocked nose, itchy, red, and watery eyes) after exposure to furred pets or pollen or a medical diagnosis of allergic rhinitis since previous questionnaire	At least 4 episodes of wheeze in the last 12 mo or at least 1 episode of wheeze with occasional or regular use of prescribed inhaled corticosteroids in the last 12 mo	Birch, cat, dog, house dust mite (<i>Dermatophagoide s pteronyssinus</i>), mold (<i>Cladosporium herbarum</i>), mugwort, timothy grass
CAPPS (Canada)	Canadian Asthma Primary Prevention Study ^{E7}	Randomized controlled study with asthma intervention	1995	80	7	Medical diagnosis of allergic rhinitis assessed at 7-y follow-up	Medical diagnosis of asthma assessed at 7-y follow-up	<i>Alternaria</i> , cat, cockroaches, dog, feathers, grass, house dust mites, mold (<i>C herbarum</i>), ragweed, trees, weeds
GINIplus (Germany) ‡	German Infant study on the influence of Nutritional Intervention plus environmental and genetic influences on allergy development ^{E8}	Population-based birth cohort. Subset for nutritional intervention	1995-1998	612	6, 10	Medical diagnosis of allergic rhinitis or hay fever during the last 12 mo	Medical diagnosis of asthma during the last 12 mo	Birch, cat, dog, house dust mite (<i>D pteronyssinus</i>), mold (<i>Cladosporium herbarum</i>), mugwort, rye, timothy grass
LISAplus (Germany) ‡	Lifestyle-related factors, Immune System and the development of Allergies in East and West Germany plus the influence of traffic emissions and genetics study ^{E9}	Population-based birth cohort	1997-1999	484	6, 10	Medical diagnosis of allergic rhinitis or hay fever during the last 12 mo	Medical diagnosis of asthma during the last 12 mo	Birch, cat, dog, house dust mite (<i>D pteronyssinus</i>), mold (<i>C herbarum</i>), mugwort, rye, timothy grass
PIAMA (The Netherlands)	Prevention and Incidence of Asthma and Mite Allergy ^{E10}	Population-based birth cohort. Subset for mattress cover intervention	1996-1997	1386	4, 8, 11/12	Sneezing, runny/blocked nose during the last 12 mo without cold or flu	Medical diagnosis of asthma during the last 12 mo	<i>Alternaria</i> , § birch, cat, <i>Dactylis</i> , dog, § house dust mite (<i>D pteronyssinus</i>)
SAGE (Canada)	Study of Asthma Genes and the Environment ^{E11}	Population-based cohort with asthma nested case-control	1995	109	8	Medical diagnosis of allergic rhinitis assessed at 8-y follow-up	Medical diagnosis of asthma assessed at 8-y follow-up	Cat, dog, feathers, grass, ragweed, trees, weeds

*Number of children with health outcome information for at least 1 time point and genotype data.

†Ages at which both rhinitis and aeroallergen sensitization data were available, and therefore allergic rhinitis could be defined.

‡Data from only the Munich center from these 2 combined German cohorts were included in the current analysis, referred to as GINI/LISA throughout the article, because genome-wide genetic data were available only for that study area (Wesel, Leipzig, and Bad Honnef were excluded).

§Available only at ages 4 and 8 y.

TABLE E2. Pooled and cohort-specific numbers of cases and controls (cases/controls)

Age (y)	Pooled	BAMSE	CAPPS	GINI/LISA	PIAMA	SAGE
Allergic rhinitis*						
4	152/1675	102/1319	-	-	50/356	-
6	80/791	-	-	80/791	-	-
7	22/58	-	22/58	-	-	-
8	437/2398	253/1426	-	-	159/888	25/84
10	125/593	-	-	125/593	-	-
11/12	154/505	-	-	-	154/505	-
16	411/828	411/828	-	-	-	-
Allergic rhinitis with concomitant asthma†						
4	37/1594	28/1246	-	-	9/348	-
6	12/780	-	-	12/780	-	-
7	9/53	-	9/53	-	-	-
8	115/2313	63/1367	-	-	37/876	15/70
10	25/585	-	-	25/585	-	-
11/12	25/502	-	-	-	25/502	-
16	69/797	69/797	-	-	-	-
Allergic rhinitis without concomitant asthma†						
4	114/1594	73/1246	-	-	41/348	-
6	68/780	-	-	68/780	-	-
7	13/53	-	13/53	-	-	-
8	318/2313	186/1367	-	-	122/876	10/70
10	98/585	-	-	98/585	-	-
11/12	129/502	-	-	-	129/502	-
16	333/797	333/797	-	-	-	-

*Age-specific controls were defined as those without allergic rhinitis.

†Age-specific controls were defined as those without allergic rhinitis or asthma.

TABLE E3. Genetic information for the 7 SNPs at the 17q21 locus

SNP	Gene	Noneffect allele/effect allele	Position (build 37)	BAMSE*		CAPPS†		GINI/LISA†		PIAMA†		SAGE†	
				N	EAFF	N	EAFF	N	EAFF	N	EAFF	N	EAFF
rs2305480	<i>GSDMB</i>	G/A	38062196	1934	0.47	80	0.47	1096	0.45	1386	0.44	109	0.40
rs7216389	<i>GSDMB</i>	C/T	38069949	1933	0.48	80	0.48	1096	0.49	1386	0.51	109	0.54
rs4065275	<i>ORMDL3</i>	A/G	38080865	1939	0.50	-	-	1096	0.50	1386	0.52	-	-
rs8076131	<i>ORMDL3</i>	A/G	38080912	1935	0.47	-	-	1096	0.45	1386	0.44	-	-
rs12603332	<i>ORMDL3</i>	T/C	38082807	1948	0.49	79	0.50	1096	0.50	1386	0.52	109	0.56
rs17608925	<i>ORMDL3</i>	T/C	38082831	1932	0.10	-	-	1096	0.11	1386	0.11	-	-
rs3744246	<i>ORMDL3</i>	C/T	38084350	1936	0.19	80	0.19	1096	0.21	1386	0.20	109	0.20

The SNPs are in linkage disequilibrium ($r^2 > 0.2$, $D' > 0.9$).

EAFF, Effect allele frequency; *GSDMB*, gasdermin B; N, number of children with health outcome information for at least 1 time point and genotype data; *ORMDL3*, ORM1-like protein 3.

*Genotypes derived from genotyped data.

†Genotypes derived from imputed data.

TABLE E4. Cohort-specific associations between 7 SNPs at the 17q21 locus and allergic rhinitis*

SNP (effect allele)	BAMSE (up to 16 y)		CAPPS (at 7 y)		GINI/LISA (up to 10 y)		PIAMA (up to 12 y)		SAGE (at 8 y)	
	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
rs2305480 (A)	1934	0.87 (0.75-1.00)	80	1.05 (0.52-2.13)	1096	0.80 (0.64-1.01)	1386	0.87 (0.72-1.06)	109	0.71 (0.36-1.40)
rs7216389 (T)	1933	1.15 (1.00-1.33)	80	0.98 (0.46-2.05)	1096	1.16 (0.93-1.44)	1386	1.14 (0.94-1.38)	109	1.25 (0.64-2.42)
rs4065275 (G)	1939	1.15 (1.00-1.33)†	-	-	1096	1.09 (0.87-1.36)	1386	1.13 (0.93-1.38)	-	-
rs8076131 (G)	1935	0.87 (0.76-1.01)	-	-	1096	0.81 (0.65-1.02)	1386	0.87 (0.71-1.06)	-	-
rs12603332 (C)	1948	1.18 (1.03-1.36)†	79	1.00 (0.47-2.12)	1096	1.09 (0.87-1.35)	1386	1.13 (0.93-1.37)	109	1.15 (0.60-2.22)
rs17608925 (C)	1932	0.97 (0.77-1.22)	-	-	1096	0.79 (0.52-1.20)	1386	0.83 (0.60-1.15)	-	-
rs3744246 (T)	1936	0.91 (0.76-1.08)	80	1.16 (0.49-2.76)	1096	0.88 (0.65-1.18)	1386	0.78 (0.61-1.00)	109	0.54 (0.21-1.40)

N, Number of children included in the model; OR, odds ratio.

*Models were adjusted for age except for CAPPS and SAGE for which only 1 time point was available. The SNPs are in linkage disequilibrium. ($r^2 > 0.2$, $D' > 0.9$).

† $P < .05$.