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PDE11A associations with asthma: Results of a genome-wide association scan

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To the Editor

The results of 4 successful genome-wide association studies have been reported recently, yielding 4 distinct loci, *ORMDL3*, *CHI3L1*, *PDE4D*, and *DENND1B*,[1–4] with the disparity in the results likely caused by differences in the phenotypes studied. In an attempt to dissect further the genetic network in complex asthmatic phenotypes, we investigated allergic asthma specifically defined in children at age 6 years. Cases were patients with allergic asthma with early-onset persistent asthma defined as having physician diagnosed asthma *and* wheeze at ages 1 and 6 years *and* asthma medication use *and* allergies as reported by the mother; controls were defined as those having no diagnosis of asthma or reactive airway disease *and* no symptoms at ages 1 or 6 years *and* no asthma medication use *and* no allergies (see Definition of Cases and Controls section in the Online Repository at www.jacionline.org for additional recruitment details and Table E1 for demographic and

Data generated by the genome-wide association studies of bipolar and schizophrenia from the Genetic Association Information Network (GAIN) were used for the analyses described in this article. The data were obtained from the database of Genotype and Phenotype (dbGaP) found at http://www.ncbi.nlm.nih.gov/gap through dbGaP accession numbers phs000017.v3.p1 and phs000021.v2.p1 for bipolar and schizophrenia, respectively.

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phenotype data). Sixty-six cases and 42 controls were successfully genotyped and analyzed by Affymetrix Genome-Wide Human Single Nucleotide Polymorphism (SNP) Array 5.0 (Affymetrix, Santa Clara, Calif) after whole-genome amplification. To test for potential population stratification, we calculated a genomic inflation factor for this study of 1.03 by using EIGENSTRAT,[5] indicating only minimal background stratification (see Statistical Analysis section in the Online Repository at www.jacionline.org).

No SNP achieved genome-wide significance using strict Bonferroni criteria for multiple testing ($0.05/396{,}207 = 1.26 \times 10^{-7}$) as the threshold of significance (see this article's Fig E1 in the Online Repository at www.jacionline.org). Overall, there were 39 SNPs with *P* values $<1 \times 10^{-4}$ for either the allelic or genotypic test, with 11 of these 39 SNPs forming 3 clusters (2 or more SNPs) in 3 discrete coding regions (Table I; see this article's Table E2 in the Online Repository at www.jacionline.org). Of the 5 SNPs selected, 4 of them were successfully genotyped in the larger collection of case (n = 104) and control (n = 503) samples (All Perinatal Risk of Asthma in Infants with Asthmatic Mothers [All PRAM]) that included the original case (n = 66) and control (n = 42) samples. The *P* values for these SNPs did not change substantially from their initial significance levels, with all *P* values within an order of magnitude from their initial value from the genome-wide association study (GWAS; Tables I and E2).

Notably, 1 SNP, rs11684634, achieved a *P* value of 8.9×10^{-7} at the first stage GWAS under the allelic association test (by Fisher exact test), which was reduced to 3.82×10^{-5} on regeno-typing of this SNP on the same subjects by using unamplified DNA via a TaqMan assay. Several inconsistent genotype calls were observed between the 2 processes (see TaqMan Genotyping section in the Online Repository at www.jacionline.org). Nevertheless, judging from the result in the extended cohort ($P = 3.4 \times 10^{-2}$; All PRAM minus the samples in the original GWAS), we regarded this SNP as potentially interesting. SNP rs11684634 is located on chromosome 2 in an intron within the *PDE11A* gene (Entrez Gene ID 50940). We resequenced all unique exons of the 4 isoforms of *PDE11A* in a subset of the GWAS cases (n = 50) on the basis of their rs11684634 genotype and all controls (n = 42). We identified 123 variants (114 SNPs and 9 insertions/deletions; see this article's Table E3 in the Online Repository at www.jacionline.org) in the 48 fragments that were sequenced to cover *PDE11A*. Four of the variants, located in 2 regions of *PDE11A*, were potentially in a high degree of linkage disequilibrium with rs11684634. Two of the 4 variants were then successfully genotyped in the extended cohort (Table I).

To attempt to replicate the association to *PDE11A*, we took a gene-centric approach[6] and queried 5 existing GWASs of asthma phenotypes for evidence for association with SNPs within *PDE11A*. Three of the 5 datasets had at least 1 SNP with a *P* value <.05 within PDE11A (Table II), with only the MRC-A/UK-C dataset not yielding a nominally significant SNP. When rs11684634 was imputed for the British 1958 Birth Cohort (B58C) dataset, a nominally significant result ($P = .046$; Table II) was obtained for this cohort among cases with asthma with onset ≥17 years of age and had the same direction of association as in the PRAM cohort. SNP rs11685634 was not significant among childhood-onset patients with asthma in the B58C cohort (Table II). The combined *P* value for rs11684634 for All PRAM and B58C adult-onset cases by using the Fisher method was 6.0×10^{-5}.

The report of an association with asthma to *PDE4D*[3] lends credence to our finding of an association within *PDE11A*, another member of the phosphodiesterase superfamily of genes. Furthermore, the same cohorts exhibiting an association to *PDE4D* also show nominal associations to SNPs within *PDE11A*, suggesting that multiple loci throughout this superfamily of genes may contribute to the susceptibility of asthma. Several

phosphodiesterase (PDE)–4 inhibitors have been found to be effective in suppressing inflammation and have been developed as potential therapies for chronic obstructive pulmonary disease and asthma.[7] *PDE3* and *PDE7* are also expressed in inflammatory cells, and *PDE5* was initially used to treat patients with exercise-induced asthma and showed bronchodilator effects.[8,9]

One major limitation of the current study is the fact that the initial discovery sample used for the GWAS is underpowered to detect loci with small effect size. We have attempted to address this issue by validating the *PDE11A* association in a larger set of cases and controls, albeit from the same study population, as well as compare our case allele frequencies to additional sets of publicly available control samples (see Table E4 in the Online Repository at www.jacionline.org), all of which validated the original findings. Furthermore, we examined the evidence for association to SNPs within *PDE11A* in 5 independent case/control populations, of which 3 had at least 1 SNP with a nominally significant *P* value. The finding of a nominal association in the B58C cohort with rs11684634 after imputation is encouraging that this SNP is of interest, and further work needs to be done to replicate this association in additional datasets. However, these results must be interpreted with caution because the association was observed only among adult-onset patients with asthma and not among the childhood-onset cases in the B58C cohort. Further, the observation that 2 additional datasets each had at least 1 SNP within *PDE11A* with a nominal association suggests the possibility of multiple variants throughout the *PDE11A* that may be contributing to the susceptibility to asthma, potentially a number of rare variants that we were underpowered to detect in this study. This is also supported by the fact that the SNPs in the replication datasets were not in linkage disequilibrium with rs11684634 (see this article's Fig E2 in the Online Repository at www.jacionline.org). The lack of overwhelming significance in the replication samples may also be a result of phenotypic heterogeneity among these populations, with both Framingham Heart Study and B58C enrolling adult-onset patients with asthma and none of the replication populations limiting their case populations to the strict phenotypic definition of childhood allergic asthma used in the PRAM study. Polymorphisms within *PDE11A* may be specific for allergic asthma, but until this specific phenotype is studied in additional populations, this conclusion cannot be drawn. In spite of this, the *PDE11A* finding is a compelling candidate gene for asthma and worth further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE I

Information on *PDE11A* SNPs genotyped in PRAM children

					GWAS				All PRAM				
rs #	**Chromosome**	**Position**	**Gene**	**Risk allele**	**Allelic***	**Genotypic***	**OR_{hom} (95% CI)**	**OR_{het} (95%CI)**	**Allelic***	**Genotypic**	**OR_{hom} (95% CI)**	**OR_{het} (95%CI)**	**Selection**
rs13428806†	2	178284927	PDE11A	A	1.98E-03	3.40E-03	4.2 (0.8–22.1)	4.0 (1.6–9.6)	1.11E-03	3.00E-03	2.4 (1.2–5.0)	2.0 (1.3–3.2)	Sequencing
rs3754993	2	178311834	PDE11A	C	9.05E-05	7.07E-04	8.5 (1.7–41.4)	3.9 (1.6–9.6)	—	—	—	—	GWAS
rs4893839	2	178312392	PDE11A	T	3.27E-06	1.70E-05	13.6 (1.6–113.3)	7.0 (2.5–19.4)	—	—	—	—	GWAS
rs11684634†	2	178314016	PDE11A	C	3.82E-05	2.51E-04	12.4 (1.5–103.5)	4.7 (1.8–11.9)	9.80E-05	3.38E-04	3.0 (1.5–6.0)	2.2 (1.4–3.5)	GWAS
rs1866210	2	178315519	PDE11A	C	6.23E-05	4.23E-04	7.7 (1.6–37.5)	4.6 (1.8–11.9)	—	—	—	—	GWAS
rs1866209	2	178315605	PDE11A	G	5.79E-06	3.81E-05	13.2 (1.6–110.0)	6.6 (2.4–18.3)	—	—	—	—	GWAS
rs998059	2	178320516	PDE11A	A	1.31E-05	1.64E-04	14.0 (1.7–115.2)	4.6 (1.8–11.7)	—	—	—	—	GWAS
rs2573088†	2	178544875	PDE11A	C	6.70E-03	8.22E-03	4.5 (1.3–15.9)	1.1 (0.3–3.3)	1.57E-03	4.24E-03	2.3 (1.2–4.4)	1.1 (0.6–2.1)	GWAS
rs9679090†	2	178587716	PDE11A	T	1.11E-02	6.00E-02	4.0 (1.2–13.0)	1.9 (0.8–4.5)	2.06E-02	1.54E-02	2.2 (1.2–4.0)	1.0 (0.6–1.7)	GWAS
rs12989423†	2	178681254	PDE11A	T	7.38E-02	1.21E-01	3.5‡ (0.9–13.0)	—	3.03E-01	3.96E-01	0.9 (0.1–7.2)	1.4 (0.8–2.4)	Sequencing

OR_{het}, Odds ratio comparing the heterozygous risk genotype to the homozygous wild-type genotype; OR_{hom}, odds ratio comparing the homozygous risk genotype to the homozygous wild-type genotype.

*P values from the Fisher exact test.

†Data presented for GWAS and All PRAM are from TaqMan genotyping.

‡Odds ratio for the autosomal-dominant situation comparing the homozygous risk and heterozygotes to the homozygous wild-type genotype. This comparison was necessary because the homozygous risk cases had a 0 cell count.

– Indicates that these SNPs were not genotyped in the All PRAM samples.

TABLE II

Replication of association within PDE11A in 3 independent cohorts

Study	Name	Chr	Position	MA	MAF	Nsubj	OR	95% CI	*P* value
CAMP	rs1405716	2	178209045	G	0.141	1205	0.75	0.59–0.96	.024
CAMP	rs1997209	2	178220601	T	0.138	1205	0.73	0.57–0.94	.012
B58C adult*	rs11684634	2	178314016	C	0.197	2211	2.19	1.15–4.17	.046‡
B58C child†	rs11684634	2	178314016	C	0.194	2274	1.24	0.63–2.46	.509
FHS	rs11687573	2	178661077	C	0.114	7477	0.81	0.67–0.98	.027

CAMP, Childhood Asthma Management Program; *FHS*, Framingham Heart Study; *MA*, minor allele; *MAF*, minor allele frequency; *Nsubj*, total number of subjects genotyped for that particular SNP; *OR*, odds ratio.

Two SNPs (rs1369518 and rs959775) within PDE11A in the Children's Health Study achieved a *P* value <.05, but because of their low MAF (<0.01), they were not considered a replication of our original finding.

*Cases were individuals with asthma onset at 17 years of age or older.

†Cases were individuals with asthma onset at 0 to 16 years of age.

‡Fisher combined *P* value for B58C and All PRAM for rs11684634 was 6.0×10^{-5}.