

Letter to the Editor

Novel childhood asthma genes interact with *in utero* and early-life tobacco smoke exposure

To the Editor:

Complex diseases, including asthma, have genetic and environmental origins. Genome-wide association studies have identified multiple genes for the development of asthma, yet they only explain a limited proportion of asthma heritability. Interactions between genetic predisposition and exposure to passive smoking might explain in part the hidden heritability of childhood asthma. However, to date, this approach has not been reported for the discovery of interactions between genes and tobacco smoke exposure.

We performed a genome-wide interaction study (GWIS) on childhood asthma to identify genes that interact with 2 well-known environmental risk factors for childhood-onset asthma: *in utero* and childhood tobacco smoke exposure. We meta-analyzed interaction results from 9 studies participating in the GABRIEL consortium¹ including more than 6,000 subjects of European descent. We replicated our findings in 4 independent studies including more than 13,000 subjects. Childhood-onset asthma was defined as asthma diagnosed by a doctor before the age of 16 years, which is consistent with the definition in the GABRIEL consortium.¹ *In utero* tobacco smoke exposure was defined as

“exposure to maternal tobacco smoking at any time during pregnancy.” Childhood tobacco smoke exposure was defined as “exposure to passive tobacco smoking at any time from birth until 16 years of age.” Details on the number of subjects, the design of the individual studies, and outcome and exposure definitions are provided in [Tables E1 to E4](#) in this article’s Online Repository at www.jacionline.org.

The effects of *in utero* tobacco smoke exposure and childhood tobacco smoke exposure were analyzed separately. All individual studies were analyzed by using a logistic regression model containing the genetic effect, the effect of tobacco smoke exposure, and an interaction term indicating the interaction between the genetic effect and tobacco smoke exposure. Further methodological considerations on GWISs and details on the statistical analyses are described in this article’s Online Repository at www.jacionline.org.

For *in utero* tobacco smoke exposure, the discovery genome-wide meta-analysis consisted of 2,654 cases and 3,073 control subjects derived from 7 studies (see [Table E1](#)). Overall, *in utero* tobacco smoke exposure increased the risk of childhood-onset asthma (see [Fig E1](#) in this article’s Online Repository at www.jacionline.org). A total of 536,705 single nucleotide polymorphisms (SNPs) were included in the interaction meta-analysis. [Fig E2](#) in this article’s Online Repository at

TABLE I. Results of the GWIS of *in utero* tobacco smoke exposure and childhood-onset asthma

Ch	SNP	Closest gene*	Type	Discovery			Replication		
				N†	OR _{int} ‡	Pf	N†	OR _{int} ‡	Pf
1	rs1674877	—	Intergenic	2654	0.51	2.19×10^{-5}	201	1.06	.89
2	rs4670230	FAM82A1	Intronic	2654	1.94	2.10×10^{-5}	201	0.78	.51
2	rs12624082	GALNT13	Intronic	2654	1.78	3.22×10^{-5}	697	1.00	.98
2	rs11684139	GALNT13	Intronic	2654	1.77	7.57×10^{-5}	697	0.85	.35
2	rs729454	—	Intergenic	2654	1.67	9.52×10^{-5}	697	1.13	.45
3	rs3856848	IL5RA	Intronic	2654	1.96	5.32×10^{-6}	201	0.59	.19
4	rs7682603	—	Intergenic	2247	0.54	1.19×10^{-5}	562	1.20	.29
5	rs1990977	RNU6ATAC2P	Intergenic	2654	2.12	7.79×10^{-5}	697	0.88	.60
5	rs4700239	—	Intergenic	2654	2.15	6.39×10^{-5}	562	0.78	.34
6	rs6456433	—	Intergenic	2654	1.99	7.99×10^{-5}	562	0.71	.15
6	rs14398	WDR46	Nonsynonymous	2654	0.45	5.44×10^{-5}	562	1.77	.01
8	rs360968	—	Intergenic	2654	0.54	5.05×10^{-5}	697	0.93	.72
9	rs943856	—	Intergenic	2654	0.59	4.94×10^{-5}	697	0.70	.04
10	rs11006296	—	Intergenic	2654	2.01	3.70×10^{-5}	562	0.84	.47
10	rs1407696	PDCD4	Intronic	2654	0.57	2.36×10^{-5}	66	0.58	.34
10	rs7079511	SHOC2	Intronic	2654	0.58	3.24×10^{-5}	697	0.98	.91
10	rs521674	ADRA2A	Upstream	2654	0.57	5.35×10^{-5}	562	1.16	.45
10	rs602618	ADRA2A	Downstream	2654	0.57	5.63×10^{-5}	562	1.15	.45
11	rs1123991	OR51E2	Synonymous	2654	0.50	6.51×10^{-5}	697	0.68	.11
11	rs3898589	CNTN5	Intronic	2654	1.83	6.11×10^{-5}	562	1.17	.40
11	rs10892848	CNTN5	Intronic	2654	1.82	5.72×10^{-5}	697	1.07	.71
12	rs706793	ACCN2	Intronic	2654	1.66	3.62×10^{-5}	697	0.75	.07
13	rs7321384	C13orf35	Intronic	2654	0.58	9.82×10^{-5}	697	0.92	.63
16	rs8051325	ANKS4B	Intronic	2654	0.47	8.37×10^{-5}	562	0.80	.37
18	rs8094633	EPB41L3	Intergenic	2654	2.13	4.29×10^{-5}	201	2.87	.03
21	rs858003	KCNJ6	Intronic	2654	1.81	8.50×10^{-5}	697	1.00	1.00
22	rs9613256	CTA-211A9.5	Within noncoding gene	2654	0.59	5.44×10^{-5}	562	1.11	.60

Ch, Chromosome; OR_{int}, odds ratio interaction; Pf, P value, fixed effect.

*Closest gene within range of 500 kb of the position of the SNP.

†Number of studies and cases included in meta-analysis.

‡Additive genetic model.

TABLE II. Results of the GWIS on childhood tobacco smoke exposure and childhood-onset asthma

Ch	SNP	Closest gene*	Type	Discovery			Replication		
				N†	OR _{int} ‡	Pf	N†	OR _{int} ‡	Pf
1	rs2026604	<i>S100A7L2</i>	Downstream	3048	1.44	7.49×10^{-5}	1003	0.83	.17
2	rs10184453	—	Intergenic	3048	1.53	8.85×10^{-5}	1003	1.18	.30
2	rs895565	—	Intergenic	3048	1.53	7.26×10^{-5}	1003	1.18	.30
2	rs11126185	—	Intergenic	3048	0.67	6.81×10^{-6}	868	1.22	.16
3	rs4234677	<i>CTD-2230D16.1</i>	Within noncoding gene	3048	0.65	6.57×10^{-5}	261	1.58	.22
3	rs264096	<i>MAGI1</i>	Intronic	3048	0.62	6.93×10^{-6}	396	0.89	.63
3	rs17239426	<i>KCNAB1</i>	Intronic	3048	0.58	7.28×10^{-5}	1003	1.18	.39
4	rs1425551	<i>IRF2</i>	Intronic	3048	1.40	6.92×10^{-5}	1003	0.98	.86
5	rs162036	<i>MTRR</i>	Nonsynonymous	3048	0.60	8.26×10^{-5}	1003	1.14	.45
5	rs7719963	—	Intergenic	3048	0.56	3.06×10^{-5}	868	0.89	.59
5	rs7447231	—	Intergenic	3048	1.55	8.36×10^{-6}	868	0.85	.31
5	rs10155635	—	Intergenic	3048	1.56	7.55×10^{-6}	261	0.62	.11
5	rs10038850	—	Intergenic	3048	1.53	1.51×10^{-5}	261	0.41	.04
5	rs10479335	—	Intergenic	3048	1.52	5.98×10^{-5}	868	0.85	.29
5	rs2312164	—	Intergenic	3048	1.42	7.18×10^{-5}	1003	0.82	.14
5	rs13357477	—	Intergenic	3048	1.58	3.59×10^{-6}	868	0.83	.24
5	rs12719549	—	Intergenic	3048	1.57	4.61×10^{-6}	868	0.82	.21
5	rs4607330	—	Intergenic	3048	1.59	2.70×10^{-6}	868	0.85	.31
6	rs441463	<i>LYRM4</i>	Intronic	3048	1.41	4.91×10^{-5}	1003	0.90	.42
6	rs1575472	<i>PACRG</i>	Intronic	3048	1.78	1.37×10^{-5}	1003	1.51	.06
7	rs17544971	<i>GRB10</i>	Intronic	3048	1.70	8.12×10^{-5}	868	1.26	.28
9	rs4977750	<i>MTAP</i>	Nonsense-mediated decay transcript	3048	0.61	1.91×10^{-5}	1003	0.93	.66
13	rs4769148	—	Intergenic	2445	0.67	4.45×10^{-5}	261	0.72	.21
13	rs12874184	—	Intergenic	3048	1.98	8.75×10^{-5}	868	1.18	.50
13	rs16972472	—	Intergenic	3048	1.79	9.59×10^{-5}	868	0.79	.32
14	rs10141836	<i>OR11G2</i>	Upstream	3048	0.70	8.89×10^{-5}	1003	0.90	.41
15	rs2602923	<i>C15orf41</i>	Intronic	3048	1.61	4.52×10^{-5}	1003	1.19	.33
16	rs13331814	<i>ZP2</i>	Intronic	3048	0.62	8.38×10^{-5}	868	0.85	.34
19	rs11085080	<i>PLIN5</i>	Intronic	3048	0.51	6.30×10^{-5}	1003	1.12	.63
20	rs6077755	<i>PSMF1</i>	Upstream	3048	1.52	6.65×10^{-6}	1003	1.11	.47
X	rs6641609	<i>PRKX</i>	Intronic	1939	0.49	3.43×10^{-5}	261	1.90	.15

Ch, Chromosome; OR_{int}, odds ratio interaction; Pf, P value, fixed effect.

*Closest gene within range of 500 kb of the position of the SNP.

†Number of cases and control subjects included in the meta-analysis.

‡Additive genetic model.

www.jacionline.org shows the Manhattan plot. We identified 27 SNPs in the discovery sample with a *P* value of less than 10^{-4} based on the fixed effect model (Table I and see Table E5 in this article's Online Repository at www.jacionline.org). Findings did not reach genome-wide significance but were consistent over all studies included, and no significant heterogeneity across studies was present (*P* value Q-statistic < .05). Four of these SNPs on chromosome 10 were in high linkage disequilibrium with each other in the discovery meta-analysis ($r^2 = 0.82$ – 0.96). The most prominent marker was located on chromosome 18 near *EPB41L3* (Forest plot, see Fig E3 in this article's Online Repository at www.jacionline.org). Table E6 in this article's Online Repository at www.jacionline.org shows the associations in exposed and nonexposed subjects. *EPB41L3* belongs to the protein 4.1 family of membrane-associated proteins, is involved in cell-cell junctions,² and might play a role in apoptosis.³ The literature shows that *in utero* tobacco smoke exposure affects the expression of genes involved in biological processes, such as cell proliferation and apoptosis, and influences lung development of the child in general.⁴ Our data suggest that this effect of *in utero* smoke exposure might potentially occur through mechanisms involving *EPB41L3* (see the additional text in this article's Online Repository).

For childhood tobacco smoke exposure, the discovery genome-wide meta-analysis consisted of 3,048 cases and 3,509 control subjects derived from 9 studies (see Table E1). Overall, childhood tobacco smoke exposure increased the risk of childhood-onset asthma (see Fig E1). A total of 538,233 SNPs were included in the interaction meta-analysis. Fig E4 in this article's Online Repository at www.jacionline.org shows the Manhattan plot. We identified 35 SNPs in the discovery sample with a *P* value of less than 10^{-4} based on the fixed effect model. Four of these SNPs were excluded because they showed heterogeneity, and the *P* value of the random effect was greater than 10^{-4} . Findings did not reach genome-wide significance. Table II and Table E7 (see this article's Online Repository at www.jacionline.org) the results for the top SNPs. Seven SNPs on chromosome 5 (except rs2312164) were in high linkage disequilibrium with each other in the discovery studies ($r^2 = 0.83$ – 1.00).

The most prominent marker was located on chromosome 6 in *PACRG* (parkin coregulated gene; Forest plot, see Fig E5 in this article's Online Repository at www.jacionline.org). Table E8 in this article's Online Repository at www.jacionline.org shows the associations in exposed and nonexposed subjects. *PACRG* is located next to and has an overlapping promoter region with parkin 2 (*PARK2*).⁵ The gene has been associated with leprosy and

parkinsonian diseases and has an important role in motile cilia function and cilia morphogenesis.^{2,6} *PACRG* is relatively highly expressed in the trachea and nasal mucosa. Ciliary dysfunction might impair mucus clearance from the airways and has been shown to affect asthma severity. Our data suggest that changes in ciliary function particularly affect the development of asthma in children exposed to passive tobacco smoke.

The genes that have been reported previously to interact with tobacco smoke exposure with respect to asthma development (ie, *TNF*,⁷ *GSTP1*,⁷ and *ADAM33*⁸) were not among our most significant hits. This can be explained by the fact that the genetic variants in these candidate gene studies have a strong main effect on asthma development. Bouzigon et al⁹ showed a more pronounced effect of the 17q21 region on the development of early-onset asthma in children with early-life tobacco smoke exposure than in those without. The genetic effect of these markers in our GWIS showed a similar direction, but the interaction was not significant.

This study on childhood asthma is the first hypothesis-free GWIS specifically aiming to identify SNPs that interact with tobacco smoke exposure in disease development. We found suggestive evidence for an interaction between rs8094633 on chromosome 18 near *EPB41L3* and *in utero* tobacco smoke exposure and an interaction between rs1575472 on chromosome 6 in *PACRG* and childhood tobacco smoke exposure. The SNPs found have not been identified previously in general genome-wide association studies on childhood asthma. Interestingly, the SNPs interacting with *in utero* and childhood tobacco smoke exposure were different and were not involved in the same pathway (see Fig E6 in this article's Online Repository at www.jacionline.org). Interactions between these SNPs and tobacco smoke exposure *in utero* and in childhood might explain part of the missing heritability of asthma. Future research needs to confirm these findings and further unravel the biological pathways.

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