2. Juniper E, O'Byrne P, Guyatt G, Ferrie P, King D. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14:902-7.
3. Juniper EF, Svensson K, Mork AC, Stahl E. Modification of the asthma quality of life questionnaire (standardised) for patients 12 years and older. Health Qual Life Outcomes 2005;3:58.
4. Perrin L, Dechamp C, Deviller P, Joly P. Reproducibility of skin tests: a comparative study of the Pepys prick test and the Morrow-Brown needle and their correlation with the serum IgE level. Clin Allergy 1984;14:581-8.
5. Crapo R. Pulmonary-function testing. N Engl J Med 1994;331:25-30.
6. Juniper E, Cockcroft D, Hargreave F. Histamine and methacholine inhalation tests. 2nd ed. Lund, Sweden: Canadian Thoracic Society and Astra Draco AB; 1994.
7. Pin I, Gibson P, Kolendowicz F, Girgis-Gabardo A, Denburg J, Hargreave F, et al. Use of induced sputum cell counts to investigate airway inflammation in asthma. Thorax 1992;47:25-9.
8. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med 2005;171:912-30.
9. Ali FR, Kay AB, Larche M. Airway hyperresponsiveness and bronchial mucosal inflammation in T cell peptide-induced asthmatic reactions in atopic subjects. Thorax 2007;62:750-7.

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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 consortium[1] 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 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

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

				Discovery			Replication		
Ch	SNP	Closest gene*	Type	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.

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 al[9] 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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Salome Scholtens, PhD[a,b]
Dirkje S. Postma, PhD[b,c]
Miriam F. Moffatt, PhD[d]
Sviatlana Panasevich, PhD[e]
Raquel Granell, PhD[f]
A. John Henderson, MD[f]
Erik Melén, PhD[e,g]
Fredrik Nyberg, PhD[e,h]
Göran Pershagen, PhD[e]
Deborah Jarvis, PhD[i]
Adaikalavan Ramasamy, PhD[i]
Matthias Wjst, PhD[j,k]
Cecilie Svanes, PhD[l]
Emmanuelle Bouzigon, PhD[m,n,o]
Florence Demenais, PhD[m,n,o]
Francine Kauffmann, PhD[p,q]
Valérie Siroux, PhD[r,s]

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

				Discovery			Replication		
Ch	SNP	Closest gene*	Type	N†	OR_{int}‡	*Pf*	N†	OR_{int} ‡	*Pf*
1	rs2026604	*S100A7L2*	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	*CTD-2230D16.1*	Within noncoding gene	3048	0.65	6.57×10^{-5}	261	1.58	.22
3	rs264096	*MAGI1*	Intronic	3048	0.62	6.93×10^{-6}	396	0.89	.63
3	rs17239426	*KCNAB1*	Intronic	3048	0.58	7.28×10^{-5}	1003	1.18	.39
4	rs1425551	*IRF2*	Intronic	3048	1.40	6.92×10^{-5}	1003	0.98	.86
5	rs162036	*MTRR*	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	*LYRM4*	Intronic	3048	1.41	4.91×10^{-5}	1003	0.90	.42
6	rs1575472	*PACRG*	Intronic	3048	1.78	1.37×10^{-5}	1003	1.51	.06
7	rs17544971	*GRB10*	Intronic	3048	1.70	8.12×10^{-5}	868	1.26	.28
9	rs4977750	*MTAP*	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	*OR11G2*	Upstream	3048	0.70	8.89×10^{-5}	1003	0.90	.41
15	rs2602923	*C15orf41*	Intronic	3048	1.61	4.52×10^{-5}	1003	1.19	.33
16	rs13331814	*ZP2*	Intronic	3048	0.62	8.38×10^{-5}	868	0.85	.34
19	rs11085080	*PLIN5*	Intronic	3048	0.51	6.30×10^{-5}	1003	1.12	.63
20	rs6077755	*PSMF1*	Upstream	3048	1.52	6.65×10^{-6}	1003	1.11	.47
X	rs6641609	*PRKX*	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.

Erika von Mutius, PhD[t]
Markus Johannes Ege, MD[t]
Charlotte Braun-Fahrländer, PhD[u,v]
Jon Genuneit, PhD[w]
the GABRIELA study group
Bert Brunekreef, PhD[x,y]
Henriette A. Smit, PhD[y,z]
Alet H. Wijga, PhD[z]
Marjan Kerkhof, PhD[a,b]
Ivan Curjuric, PhD[u,v]
Medea Imboden, PhD[u,v]
Gian A. Thun, PhD[u,v]
Nicole Probst-Hensch, PhD[u,v]
Maxim B. Freidin, PhD[aa]
Elena Iu. Bragina, PhD[aa]
I. A. Deev, PhD[bb]
V. P. Puzyrev, PhD[aa,bb]
Denise Daley, PhD[cc]
Julie Park, MMath[cc]
Allan Becker, MD[dd]
Moira Chan-Yeung, PhD[ee]
Anita L. Kozyrskyj, PhD[ff]
Peter Pare, MD[cc]
Ingo Marenholz, PhD[gg,hh]
Susanne Lau, PhD[ii]
Thomas Keil, PhD[ij]
Young-Ae Lee, PhD[gg,hh]
Michael Kabesch, PhD[kk]
Cisca Wijmenga, PhD[ll]
Lude Franke, PhD[ll]
Ilja M. Nolte, PhD[a]
Judith Vonk, PhD[a]
Ashish Kumar, PhD[u,v,mm]
Martin Farrall, PhD[mn]
William O. C. M. Cookson, PhD[d]
David P. Strachan, PhD[nn]
Gerard H. Koppelman, PhD[b,oo]
H. Marike Boezen, PhD[a,b]

From [a]the Department of Epidemiology, [b]the Groningen Research Institute for Asthma and COPD (GRIAC), [c]the Department of Pulmonology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [d]the Division of Respiratory Sciences and [i]Respiratory Epidemiology and Public Health, Imperial College, London, United Kingdom; [e]the Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [f]ALSPAC, School of Social and Community Medicine, University of Bristol, Bristol, United Kingdom; [g]Sachs' Children's Hospital, Stockholm, Sweden; [h]Global Epidemiology, AstraZeneca R&D, Mölndal, Sweden; [j]the Institute of Medical Statistics and Epidemiology (IMSE), Klinikum Rechts der Isar, Technical University, Munich, Germany; [k]Comprehensive Pneumology Center (CPC), Institute of Lung Biology and Disease (iLBD), Helmholtz Center Munich, Neuherberg, Germany; [l]Bergen Respiratory Research Group, Institute of Medicine, University of Bergen and Department of Occupational Medicine,

Haukeland University Hospital Bergen, Bergen, Norway; [m]Inserm U946, Genetic Variation and Human Diseases Unit, Paris, France; [n]Université Paris Diderot, Sorbonne Paris Cité, Institut Universitaire d'Hématologie, Paris, France; [o]Fondation Jean Dausset, Centre d'Etude du Polymorphisme Humain (CEPH), Paris, France; [p]Inserm U1018, CESP Centre for research in Epidemiology and Population Health, Respiratory and environmental epidemiology Team, Villejuif, France; [q]Université Paris Sud, UMRS 1018, Villejuif, France; [r]Inserm U823, Centre de Recherche Albert Bonniot, La Tronche, France; [s]Université Joseph Fourier, Grenoble, France; [t]LMU Munich, University Children's Hospital, Munich, Germany; [u]the Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Basel, Switzerland; [v]University of Basel, Basel, Switzerland; [w]the Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany; [x]the Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands; [y]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [z]the Centre for Prevention and Health Services Research, National Institute of Public Health and the Environment, Bilthoven, The Netherlands; [aa]the Research Institute of Medical Genetics of the Siberian Branch of Russian Academy of Medical Sciences, Tomsk, Russia; [bb]Siberian State Medical University, Tomsk, Russia; [cc]James Hogg iCAPTURE Center and [ee]the Occupational and Environmental Lung Disease Unit, University of British Columbia, Vancouver, British Columbia, Canada; [dd]Pediatrics and Child Health, University of Manitoba, Winnipeg, Manitoba, Canada; [ff]the Department of Pediatrics, Faculty of Medicine and Dentistry, University of Alberta and School of Public Health, University of Alberta, Edmonton, Canada; [gg]Pediatric Pneumology, Experimental and Clinical Research Center, [ii]Pediatric Pneumology and Immunology, and [jj]the Institute of Social Medicine, Epidemiology and Health Economics, Charité–Medical University, Berlin, Germany; [hh]Max-Delbrück-Center (MDC) for Molecular Medicine, Berlin, Germany; [kk]the Department of Paediatric Pneumology and Allergy, University Children's Hospital Regensburg (KUNO), Regensburg, Germany; [ll]the Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [mm]Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom; [nn]the Division of Population Health Sciences and Education, St George's, University of London, London, United Kingdom; and [oo]the Department of Pediatric Pulmonology and Pediatric Allergology, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. E-mail: h.m.boezen@umcg.nl.

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REFERENCES

1. Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, Heath S, et al. A large-scale, consortium-based genomewide association study of asthma. N Engl J Med 2010;363:1211-21.
2. UniProt Consortium. Reorganizing the protein space at the Universal Protein Resource (UniProt). Nucleic Acids Res 2012;40(Database issue): D71-5.
3. Dafou D, Grun B, Sinclair J, Lawrenson K, Elizabeth C, Benjamin EC, et al. Microcell-mediated chromosome transfer identifies EPB41L3 as a functional suppressor of epithelial ovarian cancers. Neoplasia 2010;12:579-89.
4. Maritz GS, Harding R. Life-long Programming implications of exposure to tobacco smoking and nicotine before and soon after birth: evidence for altered lung development. Int J Environ Res Public Health 2011;8:875-98.
5. West AB, Lockhart PJ, O'Farell C, Farrer MJ. Identification of a novel gene linked to parkin via a bi-directional promoter. J Mol Biol 2003;326:11-9.
6. Wilson GR, Wang HX, Egan GF, Robinson PJ, Delatycki MB, O'Bryan MK, et al. Deletion of the Parkin co-regulated gene causes defects in ependymal ciliary motility and hydrocephalus in the quakingviable mutant mouse. Hum Mol Genet 2010;19:1593-602.
7. Panasevich S, Lindgren C, Kere J, Wickman M, Pershagen G, Nyberg F, et al. Interaction between early maternal smoking and variants in TNF and GSTP1 in childhood wheezing. Clin Exp Allergy 2010;40:458-67.
8. Reijmerink NE, Kerkhof M, Koppelman GH, Gerritsen J, De Jongste JC, Smit HA, et al. Smoke exposure interacts with ADAM33 polymorphisms in the development of lung function and hyperresponsiveness. Allergy 2009;64:898-904.
9. Bouzigon E, Corda E, Aschard H, Dizier MH, Boland A, Bousquet J, et al. Effect of 17q21 variants and smoking exposure in early-onset asthma. N Engl J Med 2008;359:1985-94.

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Genetic variation in T_H17 pathway genes, childhood asthma, and total serum IgE levels

To the Editor:

The role of T_H17 cells and T_H17-associated cytokines in autoimmune diseases and chronic inflammation is widely recognized.[1] In children with atopic asthma, T_H17 cells in peripheral blood were found to be increased and inversely correlated with asthma control.[2] The cytokine milieu has a decisive effect on the balance between developing immunosuppressive regulatory T cells or proinflammatory T_H17 cells. Dysregulation of the cytokine balance can therefore contribute to autoimmunity and chronic inflammation.[3] IL-17A and IL-17F are signature cytokines secreted by T_H17 cells and potent inducers of inflammation. Increased levels of these cytokines were observed in airways of patients with asthma,[4] and first candidate gene studies suggested single nucleotide polymorphisms (SNPs) in *IL17A* and *IL17F* to be associated with asthma.[5,6]

This study investigated whether genetic variants in the T_H17 pathway influence asthma and total serum IgE levels during childhood. We analyzed genes involved in the differentiation and maintenance of T_H17 cells and genes coding for T_H17-related effector cytokines (Fig 1; see the Methods section in this article's Online Repository at www.jacionline.org). The relevance of associations in T_H17 pathway genes was ranked with an algorithm considering *P* values, effect sizes, and multiple testing.

Subjects (651 with asthma and 652 without asthma as controls) for association analyses with asthma and total serum IgE levels were derived from the Multicentre Asthma Genetics In Childhood Study (MAGICS, cases) and the International Study of Asthma and Allergy in Childhood, phase II (ISAAC II, reference population). Both populations were of German origin and genetically homogeneous, and the studies were performed with very similar