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IL1RL1 gene variations are associated with asthma exacerbations in children and adolescents using inhaled corticosteroids

To the editor,

Asthma, one of the most common chronic diseases in childhood, is caused by interactions between genes and environmental factors. The mainstay of treatment is daily use of inhaled corticosteroids (ICS), which are the most effective medication for controlling asthma symptoms and preventing (severe) exacerbations. ICS use reduces both hospitalizations and mortality rates[1] and improves asthma control; reflected in forced expiratory volume in 1 second (FEV_1) levels and fraction of exhaled nitric oxide (FeNO). These effects are particularly observed in asthma patients with eosinophilic, type 2 airway inflammation.[2] However, responses to ICS are heterogeneous, which while controversial, possibly reflect genetic associations.[3,4]

Genome-wide association studies (GWAS) have reproducibly found the *Interleukin 1 receptor like 1* (*IL1RL1*, *ST2*) gene to be associated with asthma susceptibility.[5] *IL1RL1* single-nucleotide polymorphisms (SNPs) and *IL1RL1* expression levels have been associated with blood eosinophils and markers of Th2 type inflammation.[6,7] However, the influence of *IL1RL1* SNPs on the effectiveness of asthma treatment has not been investigated. Since the IL-33/IL1RL1 pathway has been associated with eosinophilic, type 2, inflammation, we hypothesized that *IL1RL1* SNPs may affect corticosteroid treatment response in asthma patients. Since IL1RL1-a functions as a decoy receptor to dampen IL-33-induced signaling, genetically determined low levels of IL1RL1-a may predispose to enhanced IL-33-induced inflammation with consequently more exacerbations.

In the current study, we investigated whether *IL1RL1* gene variants are associated with asthma exacerbations (based on ER visits/hospitalizations and courses of oral corticosteroid [OCS] use), questionnaire-based asthma control and FeNO levels in asthma patients using ICS. Furthermore, we aimed to identify whether there is a pharmacogenetic effect of *IL1RL1* variants on change in FeNO levels and FEV_1% predicted in asthma patients after 4-6 weeks of ICS treatment.

After close inspection of the Linkage Disequilibrium structure of *IL1RL1*, we selected 6 *IL1RL1* SNPs that tag important LD blocks in *IL1RL1* (r^2 > .8) with SNPs previously found to be associated with asthma[5]; rs13431828, rs1041973, rs1420101, rs1946131, rs1921622, and rs10204137 (Table S1). Cross-sectional *IL1RL1* SNP discovery analysis was performed in ICS treated asthmatic children, mainly of European ancestry, from the Pharmacogenetics of Asthma Medication in Children: Medication with Anti-inflammatory effects (PACMAN) cohort (N = 820) using logistic and linear regression models. We replicated FDR corrected significant findings (P < .05) in four different cohorts collaborating within the Pharmacogenomics in Childhood Asthma (PiCA) consortium,[8] one Hispanic/Latino study; Genes-Environment and Admixture in Latino Americans (GALA II, N = 876) study, one African American population; Study of African Americans, Asthma, Genes, and Environments (SAGE, N = 525), and two European studies (≥96% European ancestry); the Effectiveness and Safety of Treatment with Asthma Therapy in children (ESTATe, N = 197) and SLOVENIA (N = 104). In addition, we performed a meta-analysis (N = 2412). The longitudinal effect of *IL1RL1* on FeNO levels and FEV_1% predicted upon ICS treatment in asthmatic children and adults was assessed in the SLOVENIA cohort. Conditional analysis was performed in PACMAN to assess the independent effects of the *IL1RL1* SNPs.

A detailed representation of the included cohorts and the allele frequencies of the *IL1RL1* SNPs are provided in Tables S2 and S3, respectively. In PACMAN, we found a significant association between four of the six SNPs (rs13431828, rs1420101, rs1921622, and rs10204137) with ER visits and "any exacerbation" (Table 1A-C), which were selected for the replication study. Sensitivity analyses on Dutch ethnicity, atopy, and medication adherence did not change these results. We did not observe an association with questionnaire-based asthma control or FeNO measurements (Table S4A-B).

In GALA II, we replicated our findings with significant results with the same direction of effect for rs13431828, rs1420101, and rs1921622 on ER visits/hospitalizations and "any exacerbation." Rs10204137 showed a significant association with "any exacerbation" (Table 1A-C). In SAGE, rs1921622 was associated with "any exacerbation" but the direction of the effect differed when compared to PACMAN. No association between *IL1RL1* and questionnaire-based asthma control was found. In the smaller SLOVENIA and ESTATe studies, no significant cross-sectional or longitudinal associations were found (Table S5).

Meta-analysis of the 4 *IL1RL1* SNPs carried through to replication showed statistically significant results for rs13431828. The C allele of rs13431828 was associated with ER visits/hospitalizations (OR = 1.32, P = .02) and increased risk of "any exacerbations" (1.31, P = .02; Table 1A-C, Figure 1). No evidence of heterogeneity was found (Q = 3.6, P = .33).

Conditional analysis in PACMAN on rs13431828, rs142010, rs1921622, and rs10204137 for "any exacerbation" indicated

that rs13431828 was the most independently associated SNP (Table S6).

These results provide new evidence that children and adolescents with the *IL1RL1* risk alleles are prone to more exacerbations than children with the protective genotypes, while using ICS. This extends previous findings that SNPs in *IL1RL1* are important in different asthma phenotypes, with more prominent effect in studies investigating childhood-onset asthma.[5] Rs1420101 has been specifically linked to the type 2-high asthma phenotype,[6] as well as to increased eosinophil numbers in peripheral blood.[9]

We observed replicable associations of the same *IL1RL1* risk alleles in the Caucasian (PACMAN) and Hispanic/Latino (GALA II) population, but not in the African American study population (SAGE). This could be due to differences in ethnicity between study groups and LD patterns in this gene, suggested by the observed differences in allele frequency between the cohorts (see Table S3). It is possible that our results may have been influenced by factors other than currently included in the model such as inhalation technique or respiratory infections, but as such data were not available in all cohorts these were not considered.

Different mechanisms may explain our findings. Firstly, *IL1RL1* SNPs may modify the asthma phenotype into a more severe phenotype, with more severe exacerbations, which are insufficiently treated with the ICS dosages prescribed to the children in this study. The risk alleles described in our study for rs13431828 (C), rs1420101 (T), rs1921622 (A), and rs10204137 (A) were previously associated with lower *IL1RL1* blood methylation levels and lower serum IL1RL1-a levels,[7] indicating that the associated SNPs are important for regulation of *IL1RL1* expression. Another mechanism to explain our results is that *IL1RL1* may have a direct pharmacogenetic interaction with steroids resulting in reduced efficacy of the steroids. Rs10204137 is a missense mutation and has been associated with increased IL1RL1-a expression, which induces *IL-33* expression and enhances IL-33 responsiveness.[10] Moreover, rs10204137 tags an LD block that contains 5 nonsynonymous coding SNPs that result in changes to four amino acids in the intracellular domain of IL1RL1-b. These coding changes affect the Toll/interleukin-1 receptor (TIR) domain of the intracellular part of the *IL1RL1* protein, which plays an important role in IL-33 induced signal transduction by *IL1RL1*. This triggers a signaling cascade that eventually results in the activation of downstream mitogen-activated protein kinases and transcription factors, such as nuclear factor kB (NF-kB) and activator protein-1.[5] Through this pathway, asthmatic children carrying the risk allele of rs10204137 may be more sensitive to IL-33. As *IL1RL1* is expressed on effector cells of the type-2 immune response such as mast cells, eosinophils, basophils, Th2 cells and ILC2 cells,[11] an increased sensitivity to IL33 will contribute to an exaggerated type-2 inflammatory response after viral or allergen exposure.

Secondly, *IL1RL1* may have a direct pharmacogenetic interaction with steroids resulting in reduced efficacy of the steroids. A recent study on ulcerative colitis found an association between dexamethasone and upregulation of soluble *IL1RL1* transcription mediated via interaction of the steroid with the glucocorticoid-responsive element in the *IL1RL1* promotor patients carrying polymorphisms.[12] To gain more insight into the mechanism underlying our finding, future studies should be performed in larger cohorts or with the use of biobank data.

This study shows that an *IL1RL1* SNP effect is present in asthmatic children using ICS. This highlights the potential investigating if novel treatment strategies targeting the IL33/IL1RL1 pathway could be used as add-on asthma treatment in patients using ICS.

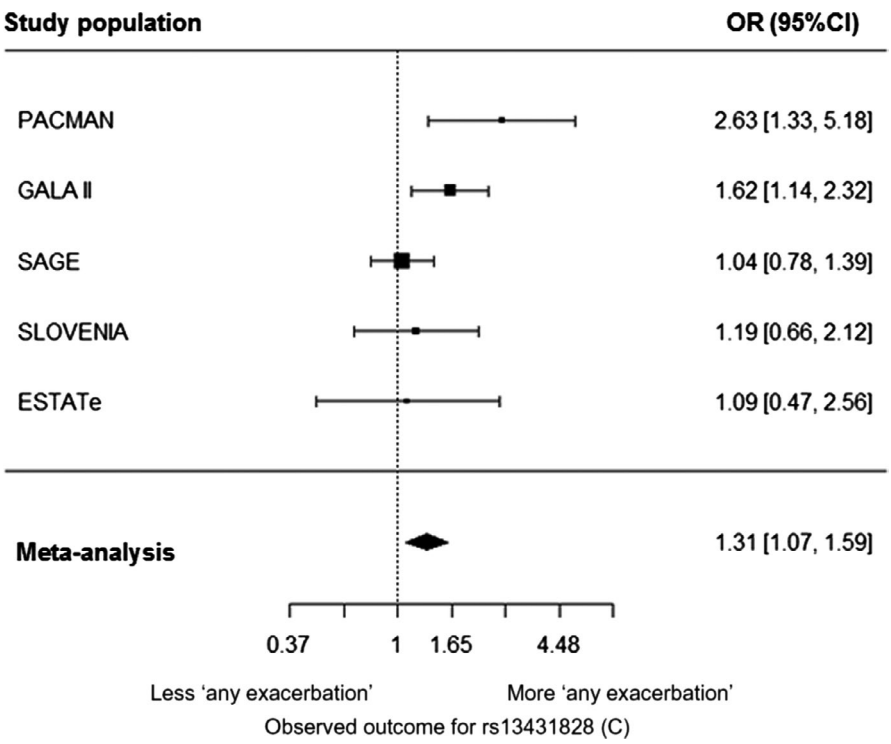

FIGURE 1 Forest plot showing the meta-analysis result of the association between the *IL1RL1* SNP rs13431828 (C) and 'any exacerbation' (P = 0.02). Included cohorts are PACMAN, GALA II, SAGE, SLOVENIA and ESTATe. Odds ratio (OR) and 95% confidence intervals (CI) are shown for the effect alleles (additive model). 'Any exacerbation' was defined as ER visits/hospitalizations and/or OCS use

TABLE 1 Results of associations of *IL1RL1* SNPs with ER visits/hospitalizations, OCS use, and "any exacerbation" per study and meta-analysis

A.										
		ER visits/hospitalisations								
		PACMAN (n = 698)			GALA II (n = 876)			SAGE (n = 525)		
SNP	Allele (R/E)[a]	OR (95% CI)	*P*	P^b	OR (95% CI)	*P*	P^b	OR (95% CI)	*P*	P^b
rs13431828	T/C	2.78 (1.11-6.94)	.02	**.04**	1.45 (1.04-2.03)	.03	**.04**	1.18 (0.88-1.58)	.26	.52
rs1041973	A/C	1.35 (0.77-2.37)	.30	.30						
rs1420101	G/A	1.61 (1.05-2.47)	.02	**.04**	1.28 (1.04-1.58)	.02	**.04**	0.90 (0.69-1.17)	.45	.60
rs1946131	G/A	1.47 (0.81-2.68)	.20	.24						
rs1921622	G/A	1.89 (1.18-3.03)	.01	**.04**	1.30 (1.06-1.59)	.01	**.04**	0.74 (0.55-0.99)	.05	.20
rs10204137	G/A	1.37 (0.87-2.16)	.18	.24	1.24 (0.99-1.56)	.06	.06	1.01 (0.76-1.35)	.92	.92
B.										
		OCS use								
		PACMAN (n = 720)			GALA II (n = 876)			SAGE (n = 525)		
SNP	Allele (R/E)[a]	OR (95% CI)	*P*	P^b	OR (95% CI)	*P*	P^b	OR (95% CI)	*P*	P^b
rs13431828	T/C	2.70 (1.08-6.79)	**.03**	.09	1.25 (0.87-1.79)	.23	.65	0.93 (0.68-1.27)	.65	.70
rs1041973	A/C	1.52 (0.86-2.66)	.15	.27						
rs1420101	G/A	1.32 (0.88-1.98)	.18	.27	1.10 (0.86-1.40)	.49	.65	0.78 (0.57-1.05)	.09	.20
rs1946131	G/A	1.08 (0.57-2.02)	.83	.83						
rs1921622	G/A	1.20 (0.78-1.86)	.41	.49	1.10 (0.88-1.38)	.44	.65	0.76 (0.54-1.08)	.10	.10
rs10204137	G/A	1.69 (1.05-2.73)	.03	.09	1.03 (0.81-1.32)	.80	.80	0.94 (0.69-1.28)	.70	.70
C.										
		Any exacerbation								
		PACMAN (n = 720)			GALA II (n = 876)			SAGE (n = 525)		
SNP	Allele (R/E)[a]	OR (95% CI)	*P*	P^b	OR (95% CI)	*P*	P^b	OR (95% CI)	*P*	P^b
rs13431828[c]	T/C	2.63 (1.33-5.18)	.006	**.03**	1.63 (1.14-2.32)	.009	.01	1.04 (0.78-1.39)	.80	.80
rs1041973	A/C	1.28 (0.84-1.96)	.26	.26						
rs1420101	G/A	1.52 (1.08-2.13)	.01	**.03**	1.35 (1.06-1.72)	.01	.01	0.83 (0.63-1.10)	.18	.36
rs1946131	G/A	1.37 (0.83-2.25)	.22	.26						
rs1921622	G/A	1.45 (1.03-2.04)	.03	**.04**	1.35 (1.08-1.70)	.009	.01	0.67 (0.50-0.90)	.009	**.03**
rs10204137[d]	G/A	1.52 (1.05-2.18)	.02	**.04**	1.29 (1.00-1.66)	.04	.04	0.91 (0.68-1.21)	.50	.66

Note: Bold-faced results are FDR corrected significant results ($P < .05$). Missing values mean the SNP was not present in the study.
Abbreviations: CI, confidence interval; ER. Emergency room; OCS, oral corticosteroid; OR, odds ratio; SNP, single-nucleotide polymorphism.
[a]R = reference allele, E = effect allele.
[b]FDR corrected *P* value.
[c]rs13431828 was not present in ESTATe, and rs3771180 was used as a surrogate marker (LD $r^2 = 1$).
[d]rs10204137 was not present in ESTATe, and rs4988956 was used as a surrogate marker (LD $r^2 = 1$).

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SLOVENIA (n = 187)			ESTATe (n = 104)			Meta-analysis (n = 2421)			
OR (95% CI)	*P*	P^b	OR (95% CI)	*P*	P^b	OR (95% CI)	*P*	P^b	N
1.20 (0.62-2.35)	.57	.77	1.01 (0.18-5.72)	.99	.99	1.32 (1.08-1.62)	.005	**.02**	2412
1.09 (0.67-1.76)	.72	.77	1.35 (0.56-3.25)	.51	.94	1.16 (1.01-1.34)	.03	.06	2412
0.93 (0.57-1.51)	.77	.77				1.13 (0.97-1.31)	.13	.17	2308
0.75 (0.46-1.22)	.24	.77	0.81 (0.34-1.94)	.63	.94	1.10 (0.95-1.29)	.18	.18	2412

SLOVENIA (n = 187)			ESTATe (n = 104)			Meta-analysis (n = 2421)			
OR (95% CI)	*P*	P^b	OR (95% CI)	*P*	P^b	OR (95% CI)	*P*	P^b	N
1.60 (0.57-4.47)	.36	.90	1.15 (0.46-2.85)	.77	.77	1.13 (0.91-1.41)	.24	.78	2412
0.95 (0.49-1.85)	.89	.90	0.68 (0.34-1.36)	.28	.77	0.98 (0.84-1.16)	.90	.90	2412
0.81 (0.41-1.59)	.54	.90				1.00 (0.84-1.18)	.96	.96	2308
1.04 (0.52-2.05)	.90	.90	1.15 (0.58-2.27)	.70	.70	1.07 (0.90-1.27)	.39	.39	2412

SLOVENIA (n = 187)			ESTATe (n = 104)			Meta-analysis (n = 2421)			
OR (95% CI)	*P*	P^b	OR (95% CI)	*P*	P^b	OR (95% CI)	*P*	P^b	N
1.19 (0.66-2.12)	.73	.83	1.09 (0.47-2.56)	.83	.86	1.31 (1.07-1.59)	.007	**.02**	2412
1.05 (0.65-1.67)	.83	.83	0.85 (0.48-1.53)	.60	.60	1.14 (0.98-1.32)	.07	.14	2412
0.84 (0.52-1.35)	.47	.83				1.08 (0.92-1.25)	.31	.31	2308
0.81 (0.50-1.30)	.38	.83	0.95 (0.53-1.70)	.86	.86	1.11 (0.96-1.30)	.14	.18	2412

CONFLICT OF INTEREST

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F. Nicole Dijk[1]
Susanne J. Vijverberg[2,3]
Natalia Hernandez-Pacheco[4,5]
Katja Repnik[6,7]
Leila Karimi[8]
Marianna Mitratza[3]
Niloufar Farzan[2,3]
Martijn C. Nawijn[9]
Esteban G. Burchard[10,11]
Marjolein Engelkes[8]
Katia M. Verhamme[8]
Uroš Potočnik[6,7]
Maria Pino-Yanes[4,5,12]
Dirkje S. Postma[13]
Anke-Hilse Maitland-van der Zee[2,3,14]
Gerard H. Koppelman[1]

[1]*Department of Pediatric Pulmonology and Pediatric Allergology, Beatrix Children's Hospital, Groningen Research Institute for Asthma and COPD (GRIAC), University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*
[2]*Department of Respiratory Medicine, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands*
[3]*Division of Pharmacoepidemiology and Clinical Pharmacology, Faculty of Science, Utrecht University, Utrecht, The Netherlands*
[4]*Research Unit, Hospital Universitario N.S. de Candelaria, Universidad de La Laguna, Santa Cruz de Tenerife, Spain*
[5]*Genomics and Health Group, Department of Biochemistry, Microbiology, Cell Biology and Genetics, Universidad de La Laguna, La Laguna, Tenerife, Spain*
[6]*Center for Human Molecular Genetics and Pharmacogenomics, Faculty of Medicine, University of Maribor, Maribor, Slovenia*
[7]*Laboratory for Biochemistry, Molecular Biology and Genomics, Faculty for Chemistry and Chemical Engineering, University of Maribor, Maribor, Slovenia*
[8]*Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands*
[9]*Laboratory of Allergology and Pulmonary Diseases, Pathology and Medical Biology, Groningen Research Institute for Asthma and COPD (GRIAC), University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*
[10]*Department of Medicine, University of California, San Francisco, CA, USA*
[11]*Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, CA, USA*
[12]*CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain*
[13]*Department of Pulmonary Diseases, Groningen Research Institute for Asthma and COPD (GRIAC), University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*
[14]*Department of Pediatric Respiratory Medicine and Allergy, Emma's Children Hospital, Academic Medical Center (AMC), University of Amsterdam, Amsterdam, The Netherlands*

Correspondence
Gerard H. Koppelman, Pediatric Pulmonology and Pediatric Allergology, Beatrix Children's Hospital, University Medical Center Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands.
Email: g.h.koppelman@umcg.nl

ORCID

F. Nicole Dijk https://orcid.org/0000-0001-7680-4951

Susanne J. Vijverberg https://orcid.org/0000-0002-4579-4081

Natalia Hernandez-Pacheco https://orcid.org/0000-0002-6313-1847

Maria Pino-Yanes https://orcid.org/0000-0003-0332-437X

Anke-Hilse Maitland-van der Zee https://orcid.org/0000-0002-0414-3442

Gerard H. Koppelman https://orcid.org/0000-0001-8567-3252

Maitland-van der Zee and Koppelman contributed equally.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Transcriptomic and methylomic features in asthmatic and nonasthmatic twins

To the editor,

Asthma is the most prevalent chronic lung inflammatory disorder characterized by reversible airflow obstruction, affecting 358 million people worldwide,[1] with aggravating factors like obesity, attention-deficit/hyperactivity disorder, socioeconomic status like poor healthcare affordability and facility, smoking and alcohol intake.[2] RNA sequencing (RNA-seq) in atopic asthma,[3] childhood asthma[4] and adult-onset severe asthma[5] has improved our understanding of cellular and molecular pathways involved. Genome-wide DNA methylation studies investigating 5-methylcytosine in CpG sites have linked methylation in lung cells with asthma endotypes and genetic risk.[6] Studies focusing on integration of genomics and interactomes have also been performed in asthma.[7] However, this multifaceted asthma phenotype together with genetic heterogeneity and environmental influences makes it challenging to fully understand the features that trigger and influence asthma development and progression. Towards addressing these challenges, we investigated transcriptomic and methylomic data in a twin cohort of asthmatic and nonasthmatic individuals.

In this exploratory study, the individuals were identified as asthmatics (GINA score ≥ 1) according to the Global Strategy for Asthma Management and Prevention guidelines (http://ginasthma.org). Participants with any viral or bacterial infections or immune disorder were excluded. All the participants with asthma were on a low dose of inhaled corticosteroid and rescue inhaler (albuterol) only. We collected PBMC from 16 female monozygotic twin pairs (5 concordant asthmatic pairs; 8 concordant nonasthmatic pairs and 3 pairs discordant for asthma) among which 13 individuals were asthmatic (GINA score 1 n = 4; 2 n = 4; 3 n = 5, Table 1). The transcriptomic RNA-seq was done on all 16 twin pairs, and the methylomic whole-genome bisulfite sequencing was done on 8 twin pairs (3 concordant asthmatic pairs; 5 concordant nonasthmatic pairs) wherein 6 individuals were asthmatics (GINA score 1 n = 1; 2 n = 1; 3 n = 4). Methods are detailed in Data S1.

Unsupervised hierarchical clustering of transcriptomic profiles shows 9/16 twin pairs clustering together, while only 2/8 twin pairs cluster together in methylomic profiles. 2/3 twin pairs discordant for asthma clustered together in transcriptomic profiles reflects