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SUPPORTING INFORMATION

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

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Coeliac disease and HLA-conferred susceptibility to autoimmunity are associated with IgE sensitization in young children

To the Editor,

The prevalence of immune-mediated diseases is continuously rising.^{1,2} In addition to genetic predisposition, socioeconomic circumstances and environmental factors may modulate the development of these diseases. Although the mechanisms leading to abnormal immune responses in autoimmune and allergic diseases may share some common pathways, the detailed pathogenesis of these conditions is still inadequately understood. The results on co-existence of allergic and autoimmune diseases have been hitherto inconsistent, some indicating co-existence^{3,4} and others the opposite or no relationship at all.^{5,6}

The aim of the current study was to examine the relationship between allergen-specific IgE (sIgE) sensitization patterns, human leucocyte antigen (HLA)-conferred disease susceptibility and autoimmunity-associated outcomes in Finland, Estonia and Russian Karelia. These three geographically adjacent areas represent socioeconomically diverse countries with only modest differences in frequencies of HLA haplotypes conferring risk for type 1 diabetes (T1D) and coeliac disease (CD),⁷ but they differ remarkably in the prevalence of immune-mediated diseases.⁸

Children born in Finland, Estonia and Russian Karelia were observed prospectively either from birth up to the age of 3 or from 3 to 5 years of age. Children in the birth cohort (BC; n = 714) carried HLA-conferred susceptibility to T1D and CD; either a combination of DR3-DQ2 and DR4-DQ8 haplotypes or alternatively DR4-DQ8/X (X = DR4-DQ8 or a neutral haplotype) or DR3-DQ2/Y (Y = DR3-DQ2 or a neutral haplotype) genotypes. Children in the young children's cohort (YCC; n = 3580) represented the general population, with no

selection based on HLA genotype. The participants were monitored for the appearance of sIgEs (≥ 0.35 kU/L) against dietary (egg, milk, peanut) and aeroallergens (cat, dog, dust mite, birch, timothy), signs of T1D-associated islet autoimmunity (IA) or CD-associated tissue transglutaminase antibody (tTGA) positivity and progression to clinical T1D or CD. Detailed methodology is provided in the Appendix S1.

A total of 37.5% of children in the BC and 39.4% in the YCC had been sensitized to at least one specific allergen during the respective follow-up (Table S1). Both cohorts showed similar proportions of dietary allergen sensitizations (88.1% vs 83.3% of the sensitised), but sensitised children in the BC were less often sensitised to aeroallergens (41.0% vs 63.6%, $P < .001$) and to both dietary and aeroallergens (29.1% vs 46.9%, $P < .001$). Finnish children developed allergen-specific sensitisation most frequently, followed by Estonian and Russian Karelian participants (Table 1). Sensitisation rates were higher among males than among females in both cohorts ($P < .02$). The distributions of HLA risk groups did not differ between sensitised and nonsensitised children in either cohort.

At the age of 3 years, 38.5% of the BC children and 30.2% of the YCC children had at least one positive sIgE ($P < .001$; Figure 1A). This difference was seen especially in Estonians (34.2% vs 27.2%, $P = .035$) and weakly in Finns (41.2% vs 35.1%, $P = .057$). A similar difference was observed for dietary allergen sensitisation at the age of 3 years (31.7% vs 24.1% in BC and YCC, respectively, $P < .001$; Figure 1B), being also present in Finns (34.7% vs 28.7%, $P = .046$) but not clearly so in Estonians (27.1% vs 21.3%, $P = .061$). Aeroallergen sensitisation at 3 years was more frequent in the BC children than in the YCC children (18.7% vs 13.1%, $P = .001$;

Figure 1C; in Finland 20.4% vs 15.5%, $P = .045$; in Estonia 16.4% vs 11.6%, $P = .048$).

When combining both cohorts, at the age of 3 years males were more frequently sensitised to at least one specific allergen compared to females (33.1% vs 29.2%, $P = .009$; dietary allergens 25.8% vs 24.3%, $P = .288$; aeroallergens 14.8% vs 12.7%, $P = .053$). Children with HLA risk genotypes for T1D and CD were more frequently sensitised compared to children with HLA risk groups associated with neutral or protective effect on the disease risk (34.2% vs 30.3%, $P = .016$); also seen in sensitisation to dietary allergens (27.8% vs 24.3%, $P = .025$), but not in sensitisation to aeroallergens (15.2% vs 13.3%, $P = .125$).

Sensitised children in both the BC and the YCC had higher odds to test positive for tTGA during their respective follow-up, compared to nonsensitised children (Table 1). In the YCC, sensitised children had also over six times the odds to be diagnosed with CD during the follow-up.

In contrast to other studies that have reported co-occurrence of atopic sensitization and T1D,^{3,4} we did not observe any correlation between sIgE sensitisation and T1D or IA. In the current study, sensitised children did, however, have higher risk for CD and tTGA positivity in contrast to a Swedish study that reported no co-existence between self-reported allergies and CD.⁶ As sIgE sensitisation at the age of 3 years was more frequent in children with HLA-conferred risk genotypes compared to children without these risk genotypes as well as compared to the general population, these results demonstrate that atopic and autoimmune diseases can be co-occurring. Our results support the idea of a common denominator in allergic and autoimmune diseases that may be especially crucial in early childhood, when the immune system is not yet fully mature. Since sIgE sensitisation was associated with HLA-conferred susceptibility to T1D and CD, but clinically only to CD and its associated autoimmunity, one might speculate that the pathomechanisms of

TABLE 1 Demographic and clinical characteristics of IgE sensitized and nonsensitized children. Values are medians and interquartile ranges if not otherwise indicated

	Birth cohort			Young children's cohort		
	sIgE sensitized n = 268	Nonsensitized n = 446	P	sIgE sensitized n = 1412	Nonsensitized n = 2168	P
Proportion of males (%)	57.8	48.2	.016	54.5	50.2	.015
Country (%)			<.001			<.001
Finland	45.6	54.4		46.0	54.0	
Estonia	32.4	67.6		36.9	63.1	
Russian Karelia	15.9	84.1		21.7	78.3	
Maternal age at birth, years	30.6 (27.1-33.8)	29.9 (25.9-33.7)	.087	30.6 (26.8-33.9)	30.1 (25.7-34.0)	.021
Number of siblings at birth	0 (0-1)	1 (0-1)	.231	0 (0-1)	1 (0-1)	.070
Gestational age, weeks	40.1 (39.3-41.0)	40.1 (39.1-41.0)	.939	40.0 (39.0-40.9)	40.0 (39.0-40.7)	.004
Caesarean section (%)	8.6	11.0	.366	21.0	19.7	.346
Birth weight, g	3610 (3230-3910)	3589 (3273-3889)	.768	3560 (3230-3930)	3534 (3200-3890)	.116
Birth length, cm	51 (49-52)	51 (50-52)	.778	51 (49-52)	51 (49-52)	.665
HLA risk group (%)			.783			.543
DR3-DQ2/ DR4-DQ8	10.1	8.5		1.9	1.4	
DR4-DQ8/ X ^a	33.6	34.1		6.3	7.0	
DR3-DQ2/ Y ^b	56.3	57.4		11.2	10.9	
Nonrisk genotypes	–	–		80.6	80.7	
Clinical outcomes [% (n)]						
Islet autoimmunity ^c	6.7 (18)	6.1 (27)	.846	6.2 (88)	4.7 (102)	.055
Type 1 diabetes	1.5 (4)	1.6 (7)	1.000	0.5 (7)	0.5 (11)	1.000
Positivity for tTGA	3.7 (10)	0.7 (3)	.008^d	1.8 (25)	0.7 (16)	.007^e
Coeliac disease	2.2 (6)	0.7 (3)	.142	1.1 (16)	0.2 (4)	<.001^f

Significant P values are bolded.

Abbreviations: 95 CI, 95% confidence interval; HLA, human leucocyte antigen; OR, odds ratio; sIgE, allergen-specific immunoglobulin E; tTGA, tissue transglutaminase antibody.

^aX = DR4-DQ8 or a neutral haplotype.

^bY = DR3-DQ2 or a neutral haplotype.

^cPositivity for insulin autoantibodies or antibodies to glutamic acid decarboxylase, islet antigen 2, or zinc transporter 8.

^dOR 5.7 (95 CI 1.6-21.0).

^eOR 2.4 (95 CI 1.3-4.6).

^fOR 6.2 (95 CI 2.1-18.6).

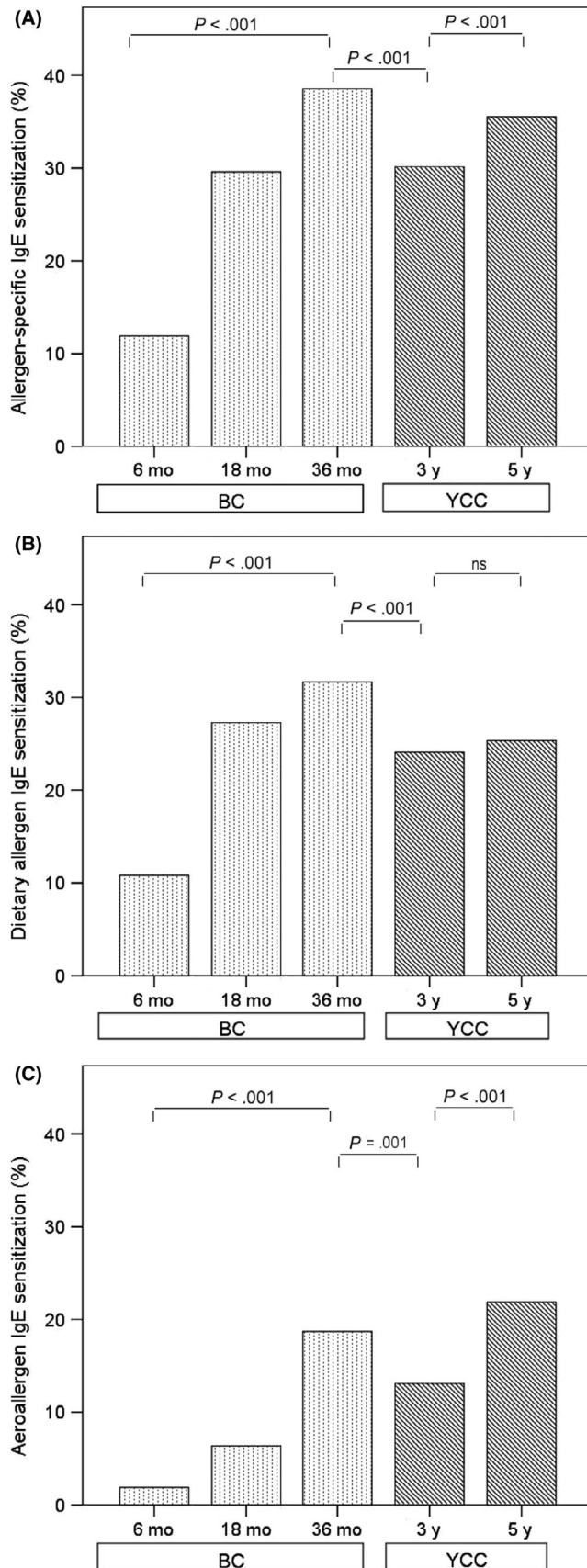


FIGURE 1 Proportion of children with allergen-specific IgE in the birth cohort (BC) at 6, 18 and 36 mo and in the young children's cohort (YCC) at 3 and 5 y of age. At 3 y of age, children in the BC, who all carried HLA-conferred risk to type 1 diabetes and coeliac disease, were more frequently sensitized to (A) any allergen ($P < .001$), (B) dietary allergen ($P < .001$), and (C) aeroallergen ($P = .001$) compared to children in the YCC who represented the general population. In both cohorts, sensitization rates increased by age, with the exception of dietary allergen sensitization between 3 and 5 y of age in the YCC

atopic sensitisation share more common pathways with CD than with T1D.

The prospective study setting, with the interesting pools of children genetically at-risk vs the general population allowed us to compare these two cohorts at the age of 3 years. One has to keep in mind that sIgE alone does not indicate clinical allergy, but together with positive skin prick tests and consistent allergy symptoms, they form a more accurate risk profile for future allergies. Poor study compliance in Russian Karelia in both cohorts was unfortunate and did not allow us to perform proper analyses between all three countries at all ages.

To conclude, we found that children carrying HLA genes predisposing to T1D and CD are more frequently sIgE sensitised at 3 years of age. We also observed that sensitisation to common allergens increases the risk of positivity for tTGA and for CD, but not for IA or T1D. The contemporaneous occurrence of atopic markers and autoimmune diseases suggests that these diseases may share some common pathogenic features.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Type I interferon suppresses memory Th2 cell cytokine secretion from allergic subjects

To the Editor,

Upper respiratory viral infections, such as rhinovirus and RSV, are major etiologic agents of allergic airway diseases and drive exacerbations of allergic asthma.¹ Viral infections elicit a variety of innate immune responses from both immune cells and nonimmune cells, and the secretion of the antiviral cytokine IFN- α/β represents the main line of innate protection. Further, IFN- α/β significantly impacts the adaptive response through effects on both T and B cells.² The immune hallmark of allergic diseases is aberrant allergen-induced type 2 inflammation, orchestrated by memory CD4⁺ T cells that produce type 2 cytokines. Our previous studies demonstrated that IFN- α could suppress the development and stability of Th2 cells

isolated from healthy nonallergic subjects.^{3,4} This observation would suggest that, under normal circumstances, IFN- α/β blocks the Th2 pathway, and this pathway may be defective in the context of the allergic state. However, the role of IFN- α in directly suppressing either Th2 development or stability in CD4⁺ T cells from allergic subjects has not been investigated. In this study, we sought to determine whether IFN- α could suppress allergic memory Th2 cells and explore the transcriptional profiles in this process by RNA sequencing.

A total of 25 subjects (age ≥ 18 years and ≤ 65 years), including 12 allergic rhinitis patients (three comorbid with asthma), four atopic asymptomatic disease-free subjects, and nine healthy subjects were enrolled. Subjects were included in the "allergic" group if they had a

Supporting information for “Coeliac disease and HLA-conferred susceptibility to autoimmunity are associated with IgE sensitisation in young children”

Methods

Study design and subjects

The prospective DIABIMMUNE study was carried out in Finland, Estonia, and Russian Karelia from 2008 to 2016. The study comprised two paediatric cohorts: a birth cohort (BC) observed from birth to the age of 3 years in which all children carried HLA-conferred susceptibility to T1D and/or CD (n=835), and a young children’s cohort (YCC) representing the general population observed from the age of 3 until the age of 5 years (n=3719).

In the BC, children were HLA-genotyped from cord blood samples at birth. Children eligible for the follow-up study had either two different disease risk associated haplotypes; a combination of (DR3)-DQA1*05-DQB1*02 (DR3-DQ2) and DRB1*04:01/02/04/05/08-DQA1*03-DQB1*03:02/4 (DR4-DQ8) haplotypes indicating a strongly increased risk for T1D or alternatively DR4-DQ8/X (X=DR4-DQ8 or a neutral haplotype) or DR3-DQ2/Y (Y=DR3-DQ2 or a neutral haplotype) genotypes indicating slightly increased T1D risk but high risk for CD. Other genotypes were either neutral or protective and not eligible for follow-up in the BC.^{1,2} The enrolled eligible children attended the study centres at the age of 3, 6, 12, 18, 24, and 36 months for clinical examination, biological samples, and for evaluation of the study diary markings, as described earlier.³ We included 714 of these children (n_{FIN}=355, n_{EST}=296, n_{RUS}=63) in the current analyses. Reasons for the exclusion were HLA misclassification (n=7), no questionnaires answered (n=31), and no IgE measurements (n=83). Of these 714 children, 552 children (77.3%) completed the 3-year follow-up. The drop-out rates differed significantly between countries, with Russian Karelia showing the highest drop-out rate of 95%. Drop-out rates for Finland and Estonia were 14.9% and 16.6%, respectively.

In the population-based YCC, HLA-genotyping was performed at the beginning of the follow-up. In contrast to the BC, all children in the YCC, regardless of HLA-genotypes, were eligible for participation in the study. Around 5% of YCC children had no reliable HLA data available (no results n=31 and inconclusive results n=161). Children attended clinical examinations with sampling of biological specimens at the age of 3 and 5 years. Children who tested positive for T1D- and/or CD-associated antibodies, and/or at least two sIgEs (≥0.35 kU/l) at the age of 3 years and their matched controls were re-examined and tested at the age of 4 years. The cases and controls were matched for age, sex, HLA-genotype, and time of the 3-year visit. In this current study we analysed data from 3580 children who had results for sIgEs at least once (n_{FIN}=1566, n_{EST}=1673, n_{RUS}=341). Since Karelian children had no sIgE measurements available at the age of 4 and 5 years, comprehensive longitudinal analyses between all three countries were not possible.

34 The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki. The
35 local ethics committees had approved the study and the parents had provided written informed consents
36 before starting the study procedures.

37 **IgE measurements**

38 Allergen-specific IgE antibodies were measured by using the ImmunoCAP® fluoroenzyme immunoassay
39 (Phadia Diagnostics, Uppsala, Sweden) according to the manufacturer's protocol. All analyses were carried
40 out blind to the knowledge of the demographic and clinical data. The cut-off for positivity for any sIgE was
41 0.35 kU/l. In the BC, sIgE for cat, egg, milk, birch, timothy, and dust mite (*Dermatophagoides pteronyssinus*)
42 were analysed at the age of 6, 18, and 36 months. IgE levels against peanut were added to the panel at the
43 age of 18 and 36 months, and against dog allergens at the age of 36 months. In the YCC, IgE against all
44 these eight allergens were analysed at the age of 3 and 5 years, and at 4 years in the case-control
45 subcohort. Children positive for at least one of the measured allergens at any visit were considered sIgE
46 sensitised and were classified into aeroallergen (cat, dog, dust mite, birch, timothy) and/or dietary allergen
47 (egg, milk, peanut) sensitised according to their sIgE profile. Sensitisation groups were not mutually
48 exclusive.

49 **Outcomes definitions**

50 T1D was defined according to the American Diabetes Association's criteria,⁴ and islet autoimmunity (IA) as
51 positivity for at least one biochemical diabetes associated autoantibody during the follow-up. These
52 autoantibodies (insulin autoantibodies, and antibodies to glutamic acid decarboxylase, islet antigen 2 and
53 zinc transporter 8) were quantified with specific radiobinding assays, as described earlier.³ Coeliac disease
54 was diagnosed according to the European Society for Paediatric Gastroenterology, Hepatology and
55 Nutrition guideline,⁵ and positivity for IgA class tissue transglutaminase antibody (tTGA) was defined as at
56 least one positive measurement during the follow-up, according to the methodology described earlier.⁶ No
57 child with coeliac disease and IgA deficiency was identified, as the children with low IgA tTGA levels tested
58 all negative for IgG tTGA, as previously reported.⁶ In both cohorts, T1D diagnoses have been regularly
59 reported to the study organization after the end of the active follow-up phase.

60 **Statistical analyses**

61 Analyses were conducted by using IBM SPSS Statistics, version 22.0 and 25.0 (IBM Corp., Armonk, N.Y.,
62 USA). Normality of the distributions of the continuous variables was assessed by using Kolmogorov-Smirnov
63 test. Categorical variables were analysed by using the Chi-square and the Fisher's exact test. The Mann-
64 Whitney U test and the Kruskal-Wallis test were used for non-parametric variables and these are marked in
65 the results with medians and interquartile range (IQR) values. McNemar's and Cochran's Q test were used
66 when analysing IgE sensitisation patterns. $P < 0.05$ was considered as statistically significant.

TABLE S1 Background data on children in the birth cohort and young children's cohort. Values are medians and interquartile ranges if not otherwise indicated.

	BC n=714	YCC n=3580	
Proportion of males (%)	51.8	51.9	68
Country (%)			69
Finland	49.7	43.7	70
Estonia	41.5	46.7	71
Russian Karelia	8.8	9.5	72
Maternal age at delivery, years	30.2 (26.6–33.7)	30.3 (26.1–33.9)	73
Number of siblings at birth	1 (0–1)	1 (0–1)	74
Gestational age, weeks	40.1 (39.3–41.0)	40.0 (39.0–40.9)	75
Caesarean section (%)	10.1	20.2	76
Birth weight, g	3590 (3260–3897)	3545 (3200–3908)	77
Birth length, cm	51 (49–52)	51 (49–52)	78
HLA risk group (%)			79
DR3-DQ2 / DR4-DQ8	9.0	1.6	80
DR4-DQ8 / X ^a	34.0	6.6	81
DR3-DQ2 / Y ^b	57.0	10.7	82
non-risk genotypes	–	81.1	83
sIgE sensitised during follow-up (%)	37.5	39.4	84
Out of the sensitised			85
Dietary allergen sensitised	88.1	83.3	86
Aeroallergen sensitised	41.0	63.6	87
Sensitized to both	29.1	46.9	88
Simultaneous sensitisation for ≥2 allergens	43.7	48.7	89
^a X=DR4-DQ8 or a neutral haplotype			90
^b Y=DR3-DQ2 or a neutral haplotype			91
BC, birth cohort; YCC, young children's cohort; HLA, human leukocyte antigen; sIgE, allergen-specific immunoglobulin E			

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