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5 Article type : Letter to the Editor

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

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11 To the Editor,

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

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

24 Children born in Finland, Estonia, and Russian Karelia were observed prospectively either from birth
25 up to the age of 3 or from 3 to 5 years of age. Children in the birth cohort (BC; n=714) carried HLA-
26 conferred susceptibility to T1D and CD; either a combination of DR3-DQ2 and DR4-DQ8 haplotypes or
27 alternatively DR4-DQ8/X (X=DR4-DQ8 or a neutral haplotype) or DR3-DQ2/Y (Y=DR3-DQ2 or a neutral
28 haplotype) genotypes. Children in the young children's cohort (YCC; n=3580) represented the general

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29 population, with no selection based on HLA genotype. The participants were monitored for the
30 appearance of sIgEs (≥ 0.35 kU/l) against dietary (egg, milk, peanut) and aeroallergens (cat, dog, dust mite,
31 birch, timothy), signs of T1D-associated islet autoimmunity (IA) or CD-associated tissue transglutaminase
32 antibody (tTGA) positivity and progression to clinical T1D or CD. Detailed methodology is provided in the
33 Supporting Information.

34 A total of 37.5% of children in the BC and 39.4% in the YCC had been sensitised to at least one
35 specific allergen during the respective follow-up (Table S1). Both cohorts showed similar proportions of
36 dietary allergen sensitisations (88.1% vs. 83.3% of the sensitised), but sensitised children in the BC were
37 less often sensitised to aeroallergens (41.0% vs. 63.6%, $P<0.001$) and to both dietary and aeroallergens
38 (29.1% vs. 46.9%, $P<0.001$). Finnish children developed allergen-specific sensitisation most frequently,
39 followed by Estonian and Russian Karelian participants (Table 1). Sensitisation rates were higher among
40 males than among females in both cohorts ($P<0.02$). The distributions of HLA risk groups did not differ
41 between sensitised and non-sensitised children in either cohort.

42 At the age of 3 years, 38.5% of the BC children and 30.2% of the YCC children had at least one
43 positive sIgE ($P<0.001$; Figure 1A). This difference was seen especially in Estonians (34.2% vs. 27.2%,
44 $P=0.035$) and weakly in Finns (41.2% vs. 35.1%, $P=0.057$). A similar difference was observed for dietary
45 allergen sensitisation at the age of 3 years (31.7% vs. 24.1% in BC and YCC respectively, $P<0.001$; Figure
46 1B), being also present in Finns (34.7% vs. 28.7%, $P=0.046$) but not clearly so in Estonians (27.1% vs.
47 21.3%, $P=0.061$). Aeroallergen sensitisation at 3 years was more frequent in the BC children than in the
48 YCC children (18.7% vs. 13.1%, $P=0.001$; Figure 1C; in Finland 20.4% vs. 15.5%, $P=0.045$; in Estonia 16.4%
49 vs. 11.6%, $P=0.048$).

50 When combining both cohorts, at the age of 3 years males were more frequently sensitised to at
51 least one specific allergen compared to females (33.1% vs. 29.2%, $P=0.009$; dietary allergens 25.8% vs.
52 24.3%, $P=0.288$; aeroallergens 14.8% vs. 12.7%, $P=0.053$). Children with HLA risk genotypes for T1D and
53 CD were more frequently sensitised compared to children with HLA risk groups associated with neutral or
54 protective effect on the disease risk (34.2% vs. 30.3%, $P=0.016$); also seen in sensitisation to dietary
55 allergens (27.8% vs. 24.3%, $P=0.025$), but not in sensitisation to aeroallergens (15.2% vs. 13.3%, $P=0.125$).

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

59 In contrast to other studies that have reported co-occurrence of atopic sensitization and T1D,^{3,4} we
60 did not observe any correlation between sIgE sensitisation and T1D or IA. In the current study, sensitised
61 children did, however, have higher risk for CD and tTGA positivity in contrast to a Swedish study that

62 reported no co-existence between self-reported allergies and CD.⁶ As sIgE sensitisation at the age of 3
63 years was more frequent in children with HLA-conferred risk genotypes compared to children without
64 these risk genotypes as well as compared to the general population, these results demonstrate that
65 atopic and autoimmune diseases can be co-occurring. Our results support the idea of a common
66 denominator in allergic and autoimmune diseases that may be especially crucial in early childhood, when
67 the immune system is not yet fully mature. Since sIgE sensitisation was associated with HLA-conferred
68 susceptibility to T1D and CD, but clinically only to CD and its associated autoimmunity, one might
69 speculate that the pathomechanisms of atopic sensitisation share more common pathways with CD than
70 with T1D.

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

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

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140 **Conflict of Interest**

141 The authors declare no conflict of interest.

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

	Birth cohort			Young children's cohort		
	sIgE sensitized n=268	Non-sensitized n=446	<i>P</i>	sIgE sensitized n=1412	Non-sensitized n=2168	<i>P</i>
Proportion of males (%)	57.8	48.2	0.016	54.5	50.2	0.015
Country (%)			<0.001			<0.001
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)	0.087	30.6 (26.8–33.9)	30.1 (25.7–34.0)	0.021
Number of siblings at birth	0 (0–1)	1 (0–1)	0.231	0 (0–1)	1 (0–1)	0.070
Gestational age, weeks	40.1 (39.3–41.0)	40.1 (39.1–41.0)	0.939	40.0 (39.0–40.9)	40.0 (39.0–40.7)	0.004
Caesarean section (%)	8.6	11.0	0.366	21.0	19.7	0.346
Birth weight, g	3610 (3230–3910)	3589 (3273–3889)	0.768	3560 (3230–3930)	3534 (3200–3890)	0.116
Birth length, cm	51 (49–52)	51 (50–52)	0.778	51 (49–52)	51 (49–52)	0.665
HLA risk group (%)			0.783			0.543

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	
non-risk genotypes	—	—		80.6	80.7	
Clinical outcomes [% (n)]						
Islet autoimmunity ^c	6.7 (18)	6.1 (27)	0.846	6.2 (88)	4.7 (102)	0.055
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)	0.008 ^d	1.8 (25)	0.7 (16)	0.007 ^e
Coeliac disease	2.2 (6)	0.7 (3)	0.142	1.1 (16)	0.2 (4)	<0.001 ^f

^a X=DR4-DQ8 or a neutral haplotype; ^b Y=DR3-DQ2 or a neutral haplotype; ^c positivity for insulin autoantibodies or antibodies to glutamic acid decarboxylase, islet antigen 2, or zinc transporter 8; ^d OR 5.7 (95CI 1.6–21.0); ^e OR 2.4 (95CI 1.3–4.6); ^f OR 6.2 (95CI 2.1–18.6)
slgE, allergen-specific immunoglobulin E; HLA, human leukocyte antigen; tTGA, tissue transglutaminase antibody; OR, odds ratio; 95CI, 95% confidence interval

1 Figure legend

2 **FIGURE 1** Proportion of children with allergen-specific IgE in the birth cohort (BC) at 6, 18, and 36 months
3 and in the young children's cohort (YCC) at 3 and 5 years of age. At 3 years of age, children in the BC, who
4 all carried HLA-conferred risk to type 1 diabetes and coeliac disease, were more frequently sensitized to
5 A) any allergen ($P<0.001$), B) dietary allergen ($P<0.001$), and C) aeroallergen ($P=0.001$) compared to
6 children in the YCC who represented the general population. In both cohorts, sensitization rates increased
7 by age, with the exception of dietary allergen sensitization between 3 and 5 years of age in the YCC.

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