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Allergies, genetic polymorphisms of Th2 interleukins and childhood acute lymphoblastic leukaemia: the ESTELLE study

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A short running title: Allergies, genetic polymorphisms and ALL

Abbreviations:

ALL	Acute lymphoblastic leukaemia
CL	Childhood acute leukaemia
GWAS	Genome wide association study
HWE	Hardy-Weinberg Equilibrium
IL	Interleukin
IRF-1	Interferon regulatory factor 1
OR	Odds ratio
RNCE	National Registry of Childhood Cancers
Treg	T-regulatory lymphocytes
ESTELLE	Study on Embryonic Tumors, Lymphomas and Leukemia in Children
ESCALE	Childhood Cancer and Leukemia Study

Abstract

Context

A negative association between a history of allergy and childhood acute lymphoblastic leukaemia (ALL) has been reported in previous studies, but remains debated. This work aimed to investigate this association accounting for genetic polymorphisms of the Th2 pathway cytokines (*IL4*, *IL10*, *IL13* and *IL4-receptor (IL4R)*).

Methods

Analyses were based on the French case-control study ESTELLE (2010-2011). The complete sample included 629 ALL cases and 1,421 population-based controls frequency-matched on age and gender. The child's medical history was collected through standardised maternal interview. Biological samples were collected, and genotyping data were available for 411 cases and 704 controls of European origin. Odds ratios (OR) were estimated using unconditional regression models adjusted for potential confounders.

Results

In the complete sample, a significant inverse association was observed between ALL and reported history of allergic rhinitis or sinusitis (OR=0.65 [0.42-0.98]; $p=0.04$), but there was no obvious association with allergies overall. There was an interaction between genetic polymorphisms in *IL4* and *IL4R* ($p_{\text{interaction}}=0.003$), as well as a gene-environment interaction between *IL4R*-rs1801275 and a reported history of asthma (IOR=0.23; $p_{\text{int}}=0.008$) and eczema (IOR= 0.47; $p_{\text{int}}=0.06$). We observed no interaction with the candidate polymorphisms in *IL4* and *IL13*.

Conclusion

These results suggest that the association between allergic symptoms and childhood ALL could be modified by *IL4R*-rs1801275, and that this variant could also interact with a functional variant in *IL4* gene. While they warrant confirmation, these results could help understand the pathological mechanisms under the reported inverse association between allergy and childhood ALL.

Keywords: Childhood leukaemia, lymphoblastic leukaemia, allergy, cytokines, gene-environment interaction, gene-gene interaction, aetiology, case-control studies, epidemiology, genetics

Introduction

Accounting for approximately one third of all childhood neoplasms in high-income countries, childhood acute leukaemia (CL) is the most common malignancy diagnosed in childhood (0-14 years), with acute lymphoblastic leukaemia (ALL) representing about 80% of childhood leukaemia¹. Some risk factors have been clearly identified, such as exposure to high-level ionizing radiation² or certain chemotherapeutic agents, Down's syndrome³ and a few rare genetic disorders⁴⁻⁷. In the current context of uncertainty on the aetiology of ALL, the immune system increasingly appears to play a significant role in leukaemogenesis for lymphoid precursors¹. It is thought that an abnormal immune response due to lack of infections during early childhood may lead to the development of CL, particularly to ALL⁸. This hypothesis meets the “hygiene hypothesis” proposed by Strachan as an explanation of the rising incidence of allergies in the Western population, which has also been related to lack of early immune stimulation⁹. While one would therefore expect a positive association between allergy history and ALL, the majority of epidemiological studies, often questionnaire-based, tended to show that children with CL had less allergies than children without CL¹⁰⁻¹³. Several studies assessed the association between allergies and CL based on objective data, with contrasting findings. An inverse association was observed in a study based on medical record¹⁴ and a study based on immunoglobulin-E levels¹⁵, but not in an American study on medical records¹⁶, nor in a Taiwanese study using medico-administrative data¹⁷. In 2011, lower levels of interleukin 10 (IL10) at birth were reported in ALL cases than in controls, suggesting an abnormal immune function at birth in ALL cases¹⁸, and findings have suggested also that two *IL10* polymorphisms were associated to ALL in Taiwan¹⁹. A meta-analysis reported this overall inverse association pattern, while highlighting the lack of consistency if a latency period was applied between the diagnosis of allergies and CL²⁰.

In our previous study, we have reported a negative association between a history of asthma or eczema and ALL that appeared to be modified by genetic polymorphisms of *IL13* and *IL10* Th2 cytokines²¹ but this remains to be confirmed with further studies on any allergy. Therefore, this study aimed to investigate the association between the risk of childhood ALL and a medical history of allergy, accounting for genetic polymorphisms of cytokines of the Th2 pathway (*IL4*, *IL10*, *IL13* and *IL4R*), which could to modify this association.

Methods

The ESTELLE study is a French national population-based case-control study conducted in 2010-2011, designed to assess the role of several environmental and genetic factors in the aetiology of childhood cancers. The design of the ESTELLE study has been described^{22,23}. Briefly, eligible children were aged less than 15 years and residing in mainland France. They were not eligible if they had been adopted (5 leukaemia cases), or if they hadn't a living French-speaker biological mother without a serious psychiatric disorder (47 cases), or if the child was in palliative care or had died (8 cases). Cases were children diagnosed with leukaemia between January 2010 and December 2011, detected and enrolled by the investigators of the National Registry of Childhood Cancers (RNCE). Controls were initially identified from a randomly-generated telephone numbers (listed and unlisted). They were children free from cancer randomly selected from the French general population over the same period, using a quota sampling method (frequency matching), based on distributions of age and sex for all childhood cancers combined expected from the national childhood registry. The quotas also ensured that the control group had the same distribution as the general population regarding the number of children aged 0-14 years living in the household, conditional on age. In total, 801 cases of leukaemia and 1,662 controls were eligible, of which 746 cases (93%), including with 635 ALL cases, and 1,421 controls (85%) participated in the ESTELLE study. Individuals with Down syndrome were excluded from these analyses (7 CL, including 6 ALL cases).

Maternal interviews were conducted over the phone using standardised questionnaires, by the same trained interviewers for cases and controls. The questionnaire elicited information on socio-demographic characteristics, childhood environment and lifestyle, medical history and childcare history. Before the interview, mothers were asked to have the child health record booklet on hand, so they could get back to the records if needed (94% for controls and 82% of ALL cases). Specific items related to the child's history of allergy and specific symptoms diagnosed by a physician, such as asthma, allergic rhinitis or sinusitis, atopic dermatitis, eczema, food allergy, allergy to medications and desensitisation. For each allergic condition or symptom, mothers were asked to report the age at its diagnosis and whether any medication (corticosteroids, antihistamines or bronchodilators) had been prescribed. For food and drug allergies, information on the specific allergens was also collected.

Biological specimens were also requested from each participant. Blood samples were taken from cases during care, and saliva samples collected at home using swab brushes for controls. Specimens were obtained from 602 ALL cases (95%) and 894 controls (63%). After DNA extraction, 499 cases and 777 controls were genotyped on a custom platform of 96 SNPs selected *a priori*, including our candidate polymorphisms in *IL4*, *IL10*, *IL13* and *IL4R*. We excluded 6 ALL cases and 2 controls who did not pass quality controls (unsuccessful genotyping or discrepancy between reported and genotyped sex). Individual call-rates ranged from 61% to 100% in cases and 88% to 100% in controls, with the vast majority being above 90% (88% in cases and 96% in controls).

In order to limit the potential for population stratification bias, all genetic analyses were restricted to participants of European origin. Indeed, having both parents born in Europe, a proxy variable derived from the reported parents' country of birth, showed to be highly predictive of the Caucasian origin in our study (sensitivity 89%, specificity 79%). This left 411 ALL cases and 704 controls genotyped and from European origin available for analyses, hereafter referred to as "genotyped sample." The study protocols complied with the French regulations and the pertinent ethical approvals were obtained.

Our analyses focussed on a set of polymorphisms selected *a priori*²¹ because of their functional impact on the respective Th2 cytokines, and they had been reported to be associated with allergy, allergic symptoms or IgE level²⁴⁻³¹: rs20541 in *IL13*, the haplotype rs2070874-rs2243250 in *IL4*, the haplotype rs1800896-rs1800871-rs1800872 in *IL10* and rs1801275 in *IL4R*.

There was no evidence for a deviation of the Hardy-Weinberg Equilibrium (HWE) for any of these candidate SNPs ($p > 0.05$). The SNP call-rates were greater than 97%.

Each polymorphism was analysed independently, under a genotypic model and following a dominant model (carrying at least one variant allele vs. none). The haplotypes for *IL4* and *IL10* were derived from available genotypes since the corresponding polymorphisms (*IL4*-rs2070874 and rs2243250; *IL10*-rs1800871 and rs1800872) have been shown to be in linkage disequilibrium³². For *IL4*, we focussed on the haplotype rs2070874-rs2243250 where CC is the reference and TT the double variant haplotype; for *IL10*, the rs1800896-rs1800871-rs1800872 haplotype CGG was the reference and TAT the triple variant haplotype of interest.

The association between allergy and ALL was analysed for each type of reported allergic symptom separately, and we also considered a category of ‘any allergy’, and of ‘possibly IgE-mediated allergies’ (asthma, allergic rhinitis/sinusitis, atopic dermatitis or food allergy)^{33,34}. Analyses were performed in the whole ESTELLE study, and repeated in the genotyped sample of European ancestry.

Odds ratios and their 95% confidence intervals were estimated using unconditional logistic regression models. All analyses were adjusted for sex, age, and other factors, such as parental professional category, maternal education level, maternal age at child’s birth, birth order, urban/rural status of the place of residence at birth, type of housing at birth and breastfeeding. The stability of the results was assessed after additional adjustments for contacts with dogs and farm animals in infancy and attendance to daycare nursery. Sensitivity analyses were also performed after applying a latency period, ignoring the allergies diagnosed in the same year as the ALL diagnosis (for cases) or recruitment (for controls). For asthma and allergic rhinitis, we also considered a specific category of children who had reportedly been prescribed antihistamines, corticoids or bronchodilators. Further analyses were carried out by ALL subtype. Interactions were assessed using likelihood ratio tests. ORs based on less than 5 exposed cases or controls are not shown. All tests were double sided; statistical significance was defined by $p < 0.05$.

The SAS software package (version 9, Cary, NC, USA) was used for all analyses.

Results

Among the case group, there were 505 precursor-B cell leukaemia, 24 Burkitt ALL, 98 T-cell ALL and 2 unspecified ALL cases. The group of 411 genotyped cases included 333 precursor-B cell leukaemia and less common subtypes such as 64 T-cell ALL, 12 Burkitt and 2 other ALL. Table 1 shows the distribution of sociodemographic characteristics in cases and controls included in the whole ESTELLE study and in the subsample of genotyped children of European ancestry. In the complete sample, the distribution of educational levels and professional category were overall similar for the cases’ and controls’ parents. However, maternal educational level was associated with the case-control status in the subsample, with mothers tending to have higher educational levels in the control group. Maternal age at birth was also associated with the case-control status in the two samples, with mothers of cases tending to be younger. Cases were more likely than controls to be first-born children, and not to have been breastfed, in broadly similar proportions in

the whole and restricted samples. The distribution of the parents' countries of birth was no different between cases and controls (not shown).

In the whole ESTELLE study, childhood ALL was not significantly associated with a history of allergy (any allergy, adjusted OR=0.91 [0.74-1.13]) (table 2). An inverse, not statistically significant, association was however observed with IgE-related allergies (OR=0.80 [0.63-1.03], $p=0.09$). No significant association was found with a history of asthma, atopic dermatitis, or eczema, but an inverse association was observed between ALL and a history of allergic rhinitis or sinusitis (OR=0.65 [0.42-0.98], $p<0.05$), which was also observed when restricting the definition of the exposition to children who reportedly took antihistamines or corticosteroids treatment. A borderline inverse association was also observed with food allergies (OR=0.62 [0.38-1.02], $p=0.06$). These associations were also observed in the genotyped subsample with the same order of magnitude, although the association with rhinitis/sinusitis no longer reached statistical significance.

When applying a latency period, similar associations were found between ALL and history of allergy but none were statistically significant (supplementary table 1). The inverse association with allergic rhinitis or sinusitis appeared more marked with B-cell precursor ALL than with T-cell ALL (supplementary table 2). These associations remained similar when excluding cases without a landline phone.

The associations between the candidate polymorphisms and ALL in the genotyped sample are presented in table 3. No significant association was observed between the genotypes of the candidate polymorphisms of the *IL10*, *IL13*, *IL4* and *IL4R* genes and ALL, including the TT variant haplotype of *IL4* (OR=0.83 [0.61-1.12], $p>0.20$) and the triple *IL10* variant haplotype TAT (OR=1.27 [0.97-1.67], $p=0.08$). There was however a gene-gene interaction between *IL4* and *IL4R* polymorphisms ($p_{\text{int}}=0.003$), with *IL4* variant haplotype being strongly associated with ALL in carriers of *IL4R*-rs1801275 variants (Interaction OR IOR=2.61 [1.39-4.91]) (Table 4).

Table 5 shows the findings of gene-environment interaction analyses between a reported history of allergy, the candidate polymorphisms and childhood ALL. We observed an inverse interaction between *IL4R*-rs1801275 genotype and a history of allergy (IOR=0.53 [0.30-0.96], $p_{\text{int}}=0.03$), and more specifically with asthma (IOR=0.23 [0.08-0.71], $p_{\text{int}}=0.008$) and eczema (IOR=0.47 [0.21-1.03], $p_{\text{int}}=0.06$). The results also suggested that there may be an interaction between *IL4* TT

haplotype and any allergy (IOR=0.49 [0.25-0.93], $p_{\text{int}}=0.03$), and between the TAT haplotype of *IL10* and atopic dermatitis (IOR=2.33 [0.88-6.23], $p_{\text{int}}=0.09$), but not with other allergic symptoms. There was no evidence of an interaction between allergy history and *IL13* polymorphism.

The associations were very similar after adjustment for attending a day-care nursery before 1 year and contact with dogs and farm animals before the age of 1 year. OR estimates were not changed after restricting genetic analyses to subjects with a call-rate of more than 90%.

Discussion

In this population-based national case-control study, there was no obvious association between ALL and allergies overall, but ALL was inversely associated with allergic rhinitis/sinusitis and food allergy. We also observed an interaction between variants of *IL4* and *IL4R*, and an interaction between *IL4R*-rs1801275 and a history of several reported allergic symptoms, such as asthma or eczema. No interaction was observed with the candidate polymorphism *IL13*-rs20541.

In the ESTELLE study, the cases identification was based on the data collection system of the French RNCE, with a high participation rate (93%), thus ensuring a relative exhaustiveness of case recruitment. Only 1% of cases were ineligible for medical reasons (palliative care or death), making survival bias very unlikely to affect our results. The controls were sampled in the French general population with the same eligibility criteria as the cases. Due to the identification of controls through a list of randomly-generated landline numbers, a selection bias could have occurred because children living in households without landline number couldn't be recruited as controls, while cases with a mobile phone only (10% of the cases) were included. However, sensitivity analyses showed similar associations between allergy and ALL after excluding cases with no landline. In the control group, the acceptance of the biological sampling was related to age and socio-demographic factors such as the maternal educational level. Hence, all models were systematically adjusted for maternal educational level and the socioprofessional category of the parents. The genotyping of cases and controls was performed using the same 96-SNP bespoke platform, not allowing to run a principal component analysis to determine the Caucasian origin. However, the restriction of analyses of genetic data to subjects born to European parents has limited a possible bias of population stratification.

The study was based on the data collected via a questionnaire that, although it was constructed to help accurate recall, relied on the memory of children's mothers, with a potential for recall bias. In this study however, 94% of the control mothers and 82% of the case mothers had their child's health records on hand during the interview, as a support to help them recall medical events accurately. Moreover, restricting the definitions of allergy history to subjects receiving corresponding treatments and considering a latency showed associations of similar magnitude, therefore going against such a bias.

A systematic adjustment was considered on potential confounders previously shown to be associated with ALL in the ESTELLE study in particular on maternal education level, birth order, urbanization level of the commune of residence, and breastfeeding, in addition to factors related to the selection of the genotyped sample. Adjusted analyses for each of these factors alone, or for all of them combined, have given very similar estimates and did not highlight any confounding effect. We cannot however rule out the possibility of residual confounding.

The size of the ESTELLE study allowed sufficient statistical power (>80%) for analysing the association between ALL and allergy history, most of which had a frequency between 10-20%. The power of gene-environment interaction analyses in genotyped subsample varied between 40% and 60% for an IOR of 2 between the interleukins polymorphisms (frequency ranging from 10% to 40%) and history of allergy (frequency ranging from 10% to 20%), which could explain some absence of significant interactions such those related to food allergy. Like other studies, the multiplicity of statistical tests performed increases the risk of first-type error and prompts cautious interpretation.

The present study found an inverse association between ALL and some reported symptoms of allergic history such as allergic rhinitis/sinusitis and food allergy, which is in line with previous findings from other interview-based studies showing that ALL cases were generally less prone to allergic symptoms than controls^{10-13,15,35-40}, and in a UK study using medical-record data¹⁴. However, other studies based on medical records or administrative data did not find this inverse association^{14-17,40}. Recall bias has been frequently discussed as a reason for the discordance of the results from previous studies, depending on the source of information (interview vs medical records). Interestingly, in the UK study from Hughes et al¹⁴, the ORs derived from medical-record data were higher than those resulting from interview data and the validity analysis showed a moderate agreement between interviews and records. When considering a latency period in

ESTELLE study, our results showed an association of the same order of magnitude, whereas in their meta-analysis including four studies with a latency period between the onset of atopy and leukaemia, Linabery et al. had reported a nearly completely attenuated association between atopy/allergy and childhood ALL³⁶.

We did not here replicate the OR of 1.3 [0.9-1.8] ($p=0.14$) between the *IL4* double-variant TT haplotype and childhood ALL that we had previously reported (ESCALE study, 2003-2004; between-study $p_{\text{int}}=0.04$)²¹. In the ESCALE study, no association was observed between ALL and *IL10* TAT haplotype, which is related to a decrease in the synthesis of cytokines, while our present findings support a slight positive association; a pooled analysis of the two datasets produced an adjusted pooled OR of 1.18 [0.97-1.44] (between-study $p_{\text{interaction}}=0.47$). Interestingly, in the NCCLS, Chang et al. found that cases of childhood ALL had lower IL10 blood levels at birth than controls, and they reported a positive association between childhood ALL and three polymorphisms in *IL10*, which is in agreement with our findings¹⁸.

In our previous study, also based on a population-based national case-control comparison), we had analysed gene-environment interaction between Th2 cytokines and allergic symptoms, with a focus on asthma and eczema²¹. This study had highlighted an inverse interaction between the *IL10* TAT haplotype and a history of asthma (IOR=0.3 [0.1-1.0]; $p_{\text{int}}=0.04$) on the risk of ALL, and noted the presence of a possible interaction between the history of asthma or eczema and *IL13*-rs20541 (IOR=1.9 [0.9-3.8]; $p_{\text{int}}=0.07$)²¹, which our current analyses do not support. In the present we observed an interaction between *IL4R*-rs1801275 genotype and a history of eczema that was not significant in ESCALE; pooling the data from ESCALE and ESTELLE, we found an adjusted pooled IOR of 0.64 [0.37-1.10], $p_{\text{int}}=0.10$ (between-study $p_{\text{int}}>0.50$).

We here report a significant gene-gene interaction between a haplotype of *IL4*, related to increased IL4 synthesis, and a variant of *IL4R*, which increases the signal transduction. In ESCALE, we had also estimated a positive interaction (IOR 1.8 [0.9-3.6])²¹; a pooled analysis of the two studies supported the presence of an *IL4 x IL4R* interaction, with an adjusted pooled IOR of 2.09 [1.33-3.28], $p=0.001$.

The IL4/IL4R signalling is implicated in human diseases including asthma, allergy, and atopic dermatitis⁴². Interestingly, the Th2 cytokine IL4 also promotes pro-metastatic phenotypes such as enhanced tumour survival and proliferation⁴³, tumour growth⁴⁴, tumour burden⁴⁵ in epithelial cancer cells, through the IL4R. Previous studies have also suggested a role of IL4 and its receptor

gene in susceptibility to autoimmune diseases such as multiple sclerosis⁴⁶ and rheumatoid arthritis⁴⁷. Further, several associations have been described between family history of autoimmune diseases and ALL^{48–50}.

In addition, two recent papers, a candidate study⁵¹ and a Genome Wide Association Study (GWAS)⁵² have identified ALL risk alleles in interferon regulatory factor (IRF). IRF-1 has been shown to play roles in the immune response⁵³, by suppressing transcription of the *IL4* gene in Th2 cells⁵⁴. The implication of this association in the aetiology of ALL need further investigation. It has also been suggested that people with allergic symptoms may have an improved immune surveillance⁵⁵. Allergic symptoms are associated with an immune system oriented towards the Th2 pathway, which could activate the humoral immune response mediated by B lymphocytes (IgE production) and eosinophils associated with a possible cytotoxic effect towards potential leukaemic clones⁵⁶. In addition, the findings of several studies on a potential association between IL10 and childhood ALL could be related to the role of T-regulatory lymphocytes (Treg) in controlling the immune responses and the secretion of IL10.

In summary, this study supports a role of *IL4R*-rs1801275 variant in the association between ALL and history of allergy and a gene-gene interaction between *IL4* and *IL4R* variants. If confirmed, these results could help understand the pathological mechanisms under the reported inverse association between allergy and childhood ALL. Further analyses in different studies and populations are needed, as well as international consortia to help unravel these relationships.

Conflict of Interest statement

The authors declare no potential conflict of interests.

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Authors' contribution

AP, MS, BN, GP, GM, CH and JC contributed to data acquisition. JC designed the study. RA, GC, JC and AB designed the analyses. RA and GC performed the analyses. RA, GC, JC and AB participated in data interpretation and drafted the manuscript. All authors critically revised the manuscript.

Data availability statement

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

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TABLE 1: Sociodemographic characteristics in cases and controls included in the whole ESTELLE study and in the subsample of genotyped children of European ancestry

	ESTELLE study						Genotyped sample							
	Controls N=1421	%	ALL N=629	%	OR	95%CI	p	Controls N=704	%	ALL N=411	%	OR	95%CI	p
Sex														
Boys	738	52	371	59				364	52	246	60			
Girls	683	48	258	41				340	48	165	40			
Age														
<1 year	196	14	19	3				83	12	14	3			
1- 2 years	267	19	152	24				129	18	111	27			
3-4 years	272	19	146	23				134	19	95	23			
5- 7 years	235	17	132	21				108	15	82	20			
8- 9 years	86	6	61	10				49	7	37	9			
10- 11 years	91	6	57	9				47	7	37	9			
12- 14 years	274	19	62	10				154	22	35	9			
Parental professional category														
Intellectual/scientific jobs, managers	942	66	399	63	1.00	Ref.		513	73	283	69	1.00	Ref.	
Employees	295	21	138	22	1.10	0.87-1.40	ns	121	17	79	19	1.22	0.88-1.70	ns
Workers and Services	184	13	92	15	1.18	0.88-1.56	ns	70	10	49	12	1.26	0.84-1.89	ns
Mother's highest diploma														
< baccalaureate	398	28	184	29	1.11	0.88-1.39	ns	155	22	110	27	1.36	1.00-1.85	0.05
baccalaureate	308	22	138	22	1.03	0.80-1.31	ns	146	21	75	18	0.91	0.66-1.28	ns
> baccalaureate	714	50	306	49	1.00	Ref.		403	57	226	55	1.00	Ref.	
Missing	1		1					-		-				
Father's highest diploma														
< baccalaureate	555	39	225	36	0.90	0.72-1.27	ns	248	35	137	33	1.02	0.77-1.37	ns
baccalaureate	269	19	116	18	0.92	0.70-1.21	ns	126	18	82	20	1.09	0.77-1.54	ns
> baccalaureate	551	39	250	40	1.00	Ref.		317	45	179	44	1.00	Ref.	
Missing	46	3	38	6				13	2	13	3%			
Maternal age at birth (years)														
<25	147	10	99	16	1.72	1.26-2.35	<0.001	59	8	49	12	1.61	1.02-2.52	0.04
25-29	455	32	216	34	1.18	0.93-1.49	ns	220	31	150	36	1.32	0.98-1.79	0.07
30-34	506	36	212	34	1.00	Ref.		265	38	146	36	1.00	Ref.	
35 or over	313	22	102	16	0.74	0.56-0.98	0.04	160	23	66	16	0.72	0.50-1.03	0.07
Place of residence at diagnosis														
Rural	577	41	247	39	1.00	Ref.		319	45	182	44	1.00	Ref.	
Intermediate	312	22	131	21	1.02	0.79-1.32	ns	161	23	86	21	1.02	0.73-1.42	ns
Urban	525	37	249	40	1.18	0.95-1.47	ns	224	32	141	34	1.14	0.86-1.53	ns
Missing	7		2					-		2				
Type of housing at birth														
Apartment	581	41	280	45	1.25	1.02-1.51	0.03	231	33	163	40	1.40	1.02-1.83	0.01
House	826	58	340	54	1.00	Ref.		463	66	243	59	1.00	Ref.	
Farm	9	1	6	1	1.69	0.57-5.02	ns	6	1	4	1	-		
Other	5		3					4	1	1				
Birth order														
1	594	42	312	50	1.00	Ref.		282	40	202	49	1.00	Ref.	
2	496	35	212	34	0.77	0.62-0.96	0.02	253	36	148	36	0.78	0.59-1.03	0.08
≥ 3	331	23	105	17	0.57	0.44-0.74	<0.0001	169	24	61	15	0.48	0.34-0.68	<0.0001
Breastfeeding														
No	541	38	280	45	1.00	Ref.		255	36	202	49	1.00	Ref.	
Yes	880	62	349	55	0.80	0.66-0.98	0.03	449	64	209	51	0.57	0.44-0.74	<0.0001

ns: p≥0.10.; Odds ratios (OR) and 95% confidence intervals (95%CI) estimated using a logistic regression model adjusted for age and sex

TABLE 2: Associations between allergy history and ALL in the whole ESTELLE study and in the genotyped sample

	ESTELLE study					Genotyped subsample				
	Controls	ALL cases		OR	95% CI	p	Controls	ALL cases		p
	N=1421	N=629					N=704	N=411	OR	
Any allergy										
No	961	416	1.00	Ref.		458	272	1.00	Ref.	
Yes	454	206	0.91	0.74-1.13	ns	244	135	0.86	0.65-1.14	ns
Missing	6	7				2	4			
IgE-related allergy										
No	1126	504	1.00	Ref.		540	328	1.00	Ref.	
Yes	287	119	0.80	0.63-1.03	0.09	160	80	0.80	0.58-1.10	ns
Missing	8	6				4	3			
Asthma										
No	1318	571	1.00	Ref.		656	376	1.00	Ref.	
Yes	99	54	1.15	0.80-1.65	ns	47	34	1.34	0.82-2.21	ns
Yes, without treatment	1	2	-			0	2	-		
Yes, with treatment	96	52	1.13	0.78-1.64	ns	46	32	1.28	0.77-2.12	ns
Antihistamines	60	23	0.79	0.47-1.32	ns	30	15	0.98	0.50-1.94	ns
Corticosteroids	72	39	1.15	0.76-1.76	ns	38	23	1.17	0.66-2.07	ns
Bronchodilators	92	51	1.16	0.80-1.69	ns	45	31	1.26	0.76-2.10	ns
Missing	4	4				1	1			
Allergic rhinitis or sinusitis										
No	1310	593	1.00	Ref.		638	385	1.00	Ref.	
Yes	105	33	0.65	0.42-0.98	0.04	64	23	0.64	0.38-1.09	0.10
Yes, without treatment	19	8	0.79	0.33-1.87	ns	10	5	0.70	0.22-2.21	ns
Yes, with treatment	84	24	0.60	0.37-0.98	0.04	54	17	0.60	0.33-1.07	0.09
Antihistamines	78	23	0.62	0.37-1.01	0.06	50	16	0.59	0.32-1.09	0.09
Corticosteroids	45	9	0.41	0.20-0.87	0.02	29	6	0.37	0.15-0.94	0.04
Missing	6	3				2	3			
Atopic dermatitis										
No	1311	585	1.00	Ref.		639	377	1.00	Ref.	
Yes	106	41	0.74	0.51-1.10	ns	64	32	0.82	0.51-1.32	ns
Missing	4	3				1	2			
Eczema										
No	1192	534	1.00	Ref.		591	345	1.00	Ref.	
Yes	225	92	0.82	0.62-1.08	ns	113	63	0.94	0.66-1.35	ns
Missing	4	3				-	3			
Food allergy										
No	1344	604	1.00	Ref.		662	396	1.00	Ref.	
Yes	73	23	0.62	0.38-1.02	0.06	40	14	0.53	0.27-1.01	0.06
Missing	4	2				2	1			
Drug allergy										
No	1326	580	1.00	Ref.		652	374	1.00	Ref.	
Yes	95	48	1.11	0.76-1.62	ns	52	36	1.28	0.79-2.06	ns
Missing	-	1				-	1			
Desensitisation										
No	1405	623	1.00	Ref.		698	406	1.00	Ref.	
Yes	13	6	1.08	0.39-2.96	ns	6	5	1.34	0.37-4.80	ns
Missing	3	-				-	-			

ns: $p \geq 0.10$; Odds ratios (OR) and 95% confidence intervals (95%CI) estimated using a logistic regression model adjusted for age, sex, maternal educational level, maternal age at child's birth, household socio-professional category, housing type, birth order, urban/rural status and breastfeeding

TABLE 3: Associations between candidate alleles of Th2 cytokines and childhood ALL, genotyped sample of 411 ALL cases and 704 controls

	Controls (N=704)		ALL cases (N=411)		OR	95% CI	p
	n	%	n	%			
IL13-rs20541							
GG	437	62.3	248	64.4	1.00	Ref.	
AG	240	34.2	123	31.9	0.92	0.68-1.20	ns
AA	24	3.4	14	3.6	0.91	0.45-1.91	ns
missing	3		26				
AG+AA vs GG	264	37.7	137	35.6	0.91	0.69-1.20	ns
IL4-rs2070874							
CC	495	70.7	297	74.4	1.00	Ref.	
CT	190	27.1	97	24.3	0.85	0.63-1.16	ns
TT	15	2.1	5	1.3	0.63	0.21-1.88	ns
missing	4		12				
CT+TT vs CC	205	29.3	102	25.6	0.84	0.62-1.13	ns
IL4-rs2243250							
CC	483	68.8	290	72.0	1.00	Ref.	
CT	203	28.9	107	26.6	0.89	0.66-1.20	ns
TT	16	2.3	6	1.5	0.73	0.27-2.02	ns
missing	2		8				
CT+TT vs CC	219	31.2	113	28.0	0.88	0.66-1.18	ns
IL4 haplotype							
No TT haplotype	496	71.0	297	75.0	1.00	Ref.	
≥1 TT	203	29.0	99	25.0	0.83	0.61-1.12	ns
missing	5		15				
IL10-rs1800896							
CC	157	22.5	85	21.6	1.00	Ref.	
CT	342	48.9	187	47.6	1.02	0.73-1.43	ns
TT	200	28.6	121	30.8	1.10	0.75-1.60	ns
missing	5		18				
CT+TT vs CC	542	77.5	308	78.4	1.05	0.76-1.44	ns
IL10-rs1800871							
GG	424	60.6	221	55.1	1.00	Ref.	
AG	239	34.1	159	39.7	1.28	0.97-1.68	0.08
AA	37	5.3	21	5.2	1.32	0.72-2.41	ns
missing	4		10				
AG+AA vs GG	276	39.4	180	44.9	1.28	0.98-1.67	0.07
IL10-rs1800872							
GG	426	60.9	224	55.9	1.00	Ref.	
GT	239	34.1	156	38.9	1.22	0.93-1.62	ns
TT	35	5.0	21	5.2	1.42	0.77-2.62	ns
missing	4		10				
GT+TT vs GG	274	39.1	177	44.1	1.25	0.95-1.63	ns
IL10 haplotype							
No TAT haplotype	422	61.0	215	55.7	1.00	Ref.	
≥1 TAT	270	39.0	171	44.3	1.27	0.97-1.67	0.08
missing	12		25				
IL4R-rs1801275							
AA	433	61.9	242	61.7	1.00	Ref.	
AG	231	33.0	134	34.2	1.03	0.78-1.37	ns
GG	36	5.1	16	4.1	0.80	0.42-1.54	ns
missing	4		19				
AG+GG vs AA	267	38.1	150	38.3	1.00	0.76-1.31	ns

ns: $p \geq 0.10$; Odds ratios (OR) and 95% confidence intervals (95%CI) estimated using a logistic regression model adjusted for age, sex, maternal educational level, maternal age at child's birth, household socio-professional category, housing type, birth order, urban/rural status and breastfeeding

TABLE 4: Gene-gene interaction analyses between candidate alleles of the Th2 cytokines pathway and ALL, genotyped sample of 411 ALL cases and 704 controls

	Without interaction		With interaction		
	OR	95% CI	OR	95% CI	p int
<i>IL13</i>-rs20541 x <i>IL4</i> TT haplotype					
Variant <i>IL13</i> -rs20541	0.95	0.71-1.26	0.95	0.67-1.34	
<i>IL4</i> haplotype TT carrier	0.83	0.60-1.14	0.83	0.54-1.29	
Variant <i>IL13</i> -rs20541 x <i>IL4</i> haplotype	-		0.99	0.52-1.87	>0.20
<i>IL13</i>-rs20541 x <i>IL10</i> TAT haplotype					
Variant <i>IL13</i> -rs20541	0.91	0.69-1.21	0.83	0.57-1.20	
<i>IL10</i> haplotype TAT carrier	1.25	0.95-1.65	1.15	0.81-1.62	
<i>IL13</i> -rs20541 x <i>IL10</i> haplotype	-		1.26	0.71-2.23	>0.20
<i>IL13</i>-rs20541 x <i>IL4R</i>-rs1801275					
Variant <i>IL13</i> -rs20541	0.93	0.70-1.22	0.99	0.69-1.41	
Variant <i>IL4R</i> -rs1801275	0.99	0.75-1.30	1.05	0.74-1.49	
Variant <i>IL13</i> -rs20541 x variant <i>IL4R</i> -rs1801275	-		0.85	0.47-1.51	>0.20
<i>IL4</i> haplotype x <i>IL10</i> haplotype					
<i>IL4</i> haplotype TT	0.81	0.59-1.10	0.64	0.42-0.98	
<i>IL10</i> haplotype TAT	1.27	0.97-1.68	1.11	0.81-1.53	
<i>IL4</i> haplotype x <i>IL10</i> haplotype	-		1.66	0.89-3.09	0.11
<i>IL4</i> haplotype x <i>IL4R</i>-rs1801275					
<i>IL4</i> haplotype TT	0.82	0.60-1.11	0.57	0.38-0.85	
Variant <i>IL4R</i> -rs1801275	0.94	0.71-1.23	0.73	0.53-1.01	
<i>IL4</i> haplotype TT x <i>IL4R</i> -rs1801275	-		2.61	1.39-4.91	0.003
<i>IL10</i> haplotype x <i>IL4R</i>-rs1801275					
<i>IL10</i> haplotype TAT	1.30	0.99-1.71	1.47	1.04-2.08	
Variant <i>IL4R</i> -rs1801275	0.98	0.74-1.29	1.12	0.78-1.61	
<i>IL10</i> haplotype TAT x <i>IL4R</i> -rs1801275	-		0.72	0.41-1.27	>0.20

Odds ratios (OR) and 95% confidence intervals (95%CI) estimated using a logistic regression model adjusted for age, sex, maternal educational level, maternal age at child's birth, household socio-professional category, housing type, birth order, urban/rural status and breastfeeding; p_{int}: p for interaction test

TABLE 5: Interaction analyses between the candidate polymorphisms and a reported history of allergy, in childhood ALL.

	Any Allergy			IgE-related allergy			Asthma			Allergic rhinitis			Eczema			Atopic dermatitis		
	OR	95% CI	<i>p</i> _{int}	OR	95% CI	<i>p</i> _{int}	OR	95% CI	<i>p</i> _{int}	OR	95% CI	<i>p</i> _{int}	OR	95% CI	<i>p</i> _{int}	OR	95% CI	<i>p</i> _{int}
<i>IL13</i>-rs20541																		
≥1 variant allele vs none	0.99	0.70-1.39		0.91	0.66-1.24		0.93	0.70-1.24		0.92	0.69-1.23		0.95	0.71-1.29		0.88	0.66-1.18	
Medical history vs none	0.91	0.64-1.30		0.77	0.51-1.17		1.46	0.78-2.72		0.67	0.34-1.31		1.01	0.63-1.62		0.69	0.37-1.30	
Variant allele x medical history	0.81	0.45-1.45	ns	1.06	0.53-2.09	ns	0.70	0.24-2.08	ns	0.96	0.32-2.85	ns	0.75	0.35-1.62	ns	1.57	0.59-4.15	ns
<i>IL4</i> TT haplotype																		
≥1 variant allele vs none	1.06	0.73-1.53		0.90	0.64-1.27		0.82	0.60-1.12		0.83	0.61-1.15		0.89	0.64-1.24		0.81	0.59-1.11	
Medical history vs none	1.00	0.72-1.39		0.87	0.60-1.27		1.23	0.69-2.19		0.67	0.36-1.26		0.98	0.64-1.51		0.73	0.41-1.30	
Variant allele x medical history	0.49	0.25-0.93	0.03	0.68	0.32-1.45	ns	1.25	0.38-4.10	ns	1.03	0.34-3.16	ns	0.61	0.26-1.44	ns	1.38	0.49-3.93	ns
<i>IL10</i> TAT haplotype																		
≥1 variant allele vs none	1.42	1.01-1.98		1.26	0.93-1.72		1.27	0.96-1.69		1.31	0.99-1.74		1.34	1.00-1.80		1.20	0.90-1.59	
Medical history vs none	0.97	0.67-1.41		0.79	0.51-1.21		1.32	0.70-2.50		0.77	0.40-1.47		1.05	0.65-1.70		0.54	0.27-1.06	
Variant allele x medical history	0.77	0.44-1.37	ns	1.11	0.57-2.15	ns	1.21	0.44-3.35	ns	0.63	0.21-1.91	ns	0.71	0.33-1.50	ns	2.33	0.88-6.23	0.09
<i>IL4R</i>-rs1801275																		
≥1 variant allele vs none	1.24	0.88-1.73		1.11	0.82-1.52		1.11	0.84-1.48		1.09	0.82-1.45		1.10	0.82-1.47		0.96	0.72-1.27	
Medical history vs none	1.07	0.74-1.53		0.96	0.62-1.47		2.27	1.21-4.25		0.93	0.46-1.91		1.15	0.72-1.83		0.62	0.32-1.21	
Variant allele x medical history	0.53	0.30-0.96	0.03	0.65	0.34-1.27	ns	0.23	0.08-0.71	0.008	0.41	0.14-1.22	ns	0.47	0.21-1.03	0.06	1.66	0.62-4.43	ns

*p*_{int}: *p* for interaction test. ns: *p*≥0.10; Odds ratios (OR) and 95% confidence intervals (95%CI) estimated using a logistic regression model adjusted for age, sex, maternal educational level, maternal age at child's birth, household socio-professional category, housing type, birth order, urban/rural status and breastfeeding