

***IL10* polymorphisms influence neonatal immune responses, atopic dermatitis, and wheeze at age 3 years**

Diana Raedler, PhD,^a Sabina Illi, PhD,^a Leonardo Araujo Pinto, MD,^b Erika von Mutius, MD,^a Thomas Illig, PhD,^{c,d} Michael Kabesch, MD,^e and Bianca Schaub, MD^a *Munich, Neuherberg, and Hannover, Germany, and Porto Alegre, Brazil*

Background: *IL10* encodes for IL-10, an important anti-inflammatory cytokine with pleiotropic effects. It is crucial for development of immune tolerance, downregulates expression of T_H1 cytokines, and is relevant for T-cell regulation. Several *IL10* single nucleotide polymorphisms (SNPs) were associated with inflammatory diseases, such as atopic diseases, which might have their onset during early immune maturation.

Objective: We hypothesized that *IL10* SNPs are associated with decreased regulatory T (Treg) cell numbers, T_H2-skewed immune responses, and decreased IFN- γ levels in cord blood parallel with increased proinflammatory markers, subsequently leading to increased atopic diseases until 3 years.

Methods: Eight genetic *IL10* variants, represented by 4 linkage disequilibrium blocks ($R^2 > 0.80$) and 2 distal promoter SNPs, were genotyped in cord blood mononuclear cells of 200 healthy neonates. Cord blood mononuclear cells were cultured unstimulated or after stimulation with lipid A, peptidoglycan, PHA, house dust mite (Der p 1), or Der p 1 plus lipid A. mRNA expression of Treg cell-associated genes (forkhead box protein P3 [*FOXP3*], glucocorticoid-induced TNF receptor [*GITR*], lymphocyte activation gene 3 [*LAG3*]), T_H1/T_H2 cytokines, TNF- α , and GM-CSF were assessed. Atopic and respiratory outcomes (atopic dermatitis [AD] and wheeze) were assessed by means of questionnaire at age 3 years.

Results: Carriers of 3 *IL10* SNP blocks and both distal promoter SNPs showed reduced expression of Treg cell markers, reduced IL-5 levels, proinflammatory TNF- α and GM-CSF, and partially increased IFN- γ levels. The same SNPs presented as determinant for AD, wheeze, or symptoms of AD, wheeze, or both at age 3 years.

Conclusions: Polymorphisms in *IL10* influenced Treg cell marker expression and T_H1/T_H2 and proinflammatory cytokine secretion early in life. This was relevant for further development of immune-mediated diseases, such as AD and wheeze, in early childhood. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

Key words: Atopy, atopic dermatitis, cord blood, cytokines, *IL-10*, single nucleotide polymorphisms, regulatory T cells, wheeze

Human IL-10 is a protein of 160 amino acids existing as a 37-kDa homodimer.¹ IL-10 is a pleiotropic cytokine produced by a variety of cells, such as T_H1, T_H2, and a subset of T_H17 lymphocytes, B cells, eosinophils, mast cells, myeloid dendritic cells, and alveolar macrophages.² Additionally, IL-10 is produced by “conventional” regulatory T (Treg) cells, certain T_H3 clones, and regulatory T_R1 cells,²⁻⁴ where IL-10 can drive the conversion of conventional T cells to T_R1 cells.⁵ For T_H1 and T_H17 cells, production of IL-10 serves as a negative feedback regulator that controls numerous immune responses and prevents tissue damage.⁴

IL-10 has important immune regulatory functions that influence a variety of cells of the immune system.⁶ IL-10 was initially known as cytokine synthesis-inhibiting factor⁷ based on its biological activity because IL-10 inhibits cytokine production by T_H1 and T_H2 lymphocytes, mononuclear phagocytes, and natural killer cells.⁸ It downregulates the proinflammatory cytokines IL-1 β , IL-6, IL-8, TNF- α , and GM-CSF.⁹ Moreover, IL-10 inhibits the function of antigen-presenting cells because it blocks the maturation of dendritic cells and downregulates expression of MHC II and costimulatory molecules.¹⁰ In addition to the immunosuppressive effect of IL-10 on macrophages, monocytes, and T cells,⁹ it enhances B-cell proliferation, differentiation, and antibody production. Because IL-10 can regulate cellular and humoral immunity, it became a candidate gene in the regulation of autoimmune/inflammatory diseases.⁹ The *IL10* gene is approximately 5.1 kB in size,¹¹ comprises 5 exons, and is located on chromosome 1q31-32, a genomic region linked to asthma and related phenotypes.¹² Single nucleotide polymorphisms (SNPs) in *IL10* were shown to be associated with asthma^{9,12-14} but also systemic lupus erythematosus,¹⁵ rheumatoid arthritis,¹⁶ psoriasis,¹⁷ and infectious diseases.¹⁸ Common to all these diseases is their potential regulation by T cells, including Treg cells. However, the effect of *IL10* SNPs on T-cell regulation has not been investigated related to atopic diseases, particularly during early immune development.

In this study we aimed to assess the effect of *IL10* SNPs on T_H1/T_H2 lineage and proinflammatory cytokines and Treg

From ^aUniversity Children's Hospital Munich, Department of Pulmonary and Allergy, LMU Munich; ^bInstituto de Pesquisas Biomédicas, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre; ^cthe Institute of Epidemiology, Helmholtz Centre Munich, German Research Centre for Environmental Health, Neuherberg; and ^dHannover Unified Biobank and ^ethe Clinic for Paediatric Pneumology, Allergology and Neonatology, Hannover Medical School.

Supported by Bavarian Research Association PIZ-140-08 (to B.S.) and the German Research Foundation as part of the transregional collaborative research program TR22 “allergic immune responses of the lung,” grant DFG SFB TR22/A22 (to D.R. and B.S.). Further funding was provided by the Comprehensive Pulmonary Centre (CPC for B.S.) and by the German Ministry of Education and Research (BMBF) as part of the National Genome Research Network (NGFN), with grant NGFN 01GS0810 (to L.A.P. and M.K.). Genotyping was performed in collaboration with the Genome Analysis Centre of the Helmholtz Centre Munich.

Disclosure of potential conflict of interest: E. von Mutius is a consultant for Novartis, GlaxoSmithKline, ALK-Abelló, and Protectimmun; has received speakers' fees from InfectoPharm; has been supported by Airsonett AB; is a member of the expert panel for the UK Research Excellence Framework; and is an Associate Editor of the *Journal of Allergy and Clinical Immunology*. M. Kabesch has financial interests in Roxall, GlaxoSmithKline, Novartis, Sanofi Aventis, Allergopharma, and AstraZeneca GmbH and has been supported by Deutsche Forschungsgemeinschaft (DFG), the BMBF, and the European Union (EU). B. Schaub has been supported by DFG and the EU. The rest of the authors declare that they have no relevant conflicts of interest. Received for publication January 3, 2012; revised July 30, 2012; accepted for publication August 8, 2012.

Corresponding author: Bianca Schaub, MD, University Children's Hospital Munich, Lindwurmstr 4, 80337 Munich, Germany. E-mail: Bianca.Schaub@med.uni-muenchen.de.

0091-6749/\$36.00

© 2012 American Academy of Allergy, Asthma & Immunology
<http://dx.doi.org/10.1016/j.jaci.2012.08.008>

Abbreviations used

AD:	Atopic dermatitis
CBMC:	Cord blood mononuclear cell
FOXP3:	Forkhead box protein P3
GITR:	Glucocorticoid-induced TNF receptor
HWE:	Hardy-Weinberg equilibrium
LAG3:	Lymphocyte activation gene 3
LD:	Linkage disequilibrium
LpA:	Lipid A
Ppg:	Peptidoglycan
SNP:	Single nucleotide polymorphism
TLR:	Toll-like receptor
Treg:	Regulatory T

cell-associated genes in cord blood. We further aimed to determine whether *IL10* SNPs subsequently have a potential role in the development of immune-mediated diseases, such as atopic dermatitis (AD) or wheeze, until the age of 3 years.

METHODS**Study population**

Umbilical cord blood ($n = 200$; 72 samples from atopic mothers and 128 samples from nonatopic mothers) was obtained from neonates born in the Munich metropolitan area of Germany. Subjects were recruited from July 2005 to September 2007 during the last trimester of pregnancy (for details, see the [Methods](#) section in this article's Online Repository at www.jacionline.org). Our previous studies showed that maternal atopy negatively affects Treg cell quantity and function in cord blood.^{19,20} Maternal atopy was defined as a doctor's diagnosis of asthma and/or eczema and/or hay fever. Maternal total and specific IgE (RAST) levels were measured. A positive specific IgE level was defined as 0.35 IU/mL or greater to 1 or more common allergens from a panel of 20. The laboratory investigators were blinded to clinical information; samples were analyzed based on sample availability to perform the laboratory studies. Informed consent was obtained from the mothers for their participation in the study, including cord blood collection. Approval was obtained from the human ethics committee of the Bavarian Ethical Board, LMU Munich, Germany. Two hundred children were recruited; the number for the single analyses varied because of sample availability or nonparticipation in the follow-up.

Follow-up at the age of 3 years

A follow-up by parental questionnaire was performed. The outcomes included AD, wheeze, and food allergy. A positive allergen test result was based on parental reporting of a positive blood or skin test result. Wheeze and AD were defined by respective symptoms within the last 36 months.

Polymorphisms selection and genotyping

Tagging SNPs were selected based on the American (CEU) and European (TSI) population samples genotyped in the HapMap project. All SNPs located from the proximal promoter (-4000 bp) to the 3' untranslated region and with a minor allele frequency of greater than 0.1 in both populations were included in the analyses. Polymorphisms with R^2 values of 0.8 or greater were defined as a linkage disequilibrium (LD) block ([Fig 1](#)). By using Haploview (Version 3.32, MIT, www.broad.mit.edu/mpg/haploview), 4 tagging SNPs (rs1800890, rs1800871, rs1878672, and rs3024498) were selected from all 13 frequent polymorphisms located in the *IL10* region ([Fig 1](#)). Two further polymorphisms, rs1800893 and rs3024496, which are in close LD with rs1878672, and 2 putative functional variations, rs79309463 (deletion) and rs10494879, which are located in the promoter (-7616 and -6424 bp), were genotyped.²¹⁻²⁴ In total, 7 polymorphisms and 1 deletion were investigated. The LD plot of all 8 polymorphisms within our study population is shown in [Fig E1](#) in this article's Online Repository at www.jacionline.org. Genotyping was performed by using

matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Sequenom, San Diego, Calif).²⁵ PCR assays and associated extension reactions were designed with the SpectroDESIGNER software (Sequenom). All amplification and extension reaction conditions have been previously described.²⁶ Deviations from Hardy-Weinberg equilibrium (HWE) were assessed for quality control of genotyping procedures. Allele frequencies were compared with the HapMap Centre d'Etude du Polymorphisme Humain population.

Isolation, culture, and real-time RT-PCR of cord blood mononuclear cells

Cord blood was collected from the umbilical vein after delivery and processed within 24 hours. Cord blood mononuclear cells (CBMCs) were isolated by using density gradient centrifugation with Ficoll-Hypaque and cultured unstimulated or stimulated with lipid A (LpA; 0.1 μ g/mL), peptidoglycan (Ppg; 10 μ g/mL), PHA (5 μ g/mL), *Dermatophagoides pteronyssinus* (Der p 1, 30 μ g/mL), or a combination of LpA and Der p 1, as previously described.²⁰ Immune responses of unstimulated cells reflect the basal state, whereas the Toll-like receptor (TLR) agonists LpA (TLR4) and Ppg (TLR2/NOD2) as innate stimuli and the allergen Der p 1 were chosen because of their relevance in allergic diseases and immune responses, such as lymphocyte proliferation and cytokine secretion, respectively.²⁷⁻³⁰ The combination of innate stimulus and allergen was used to mimic one part of the natural farm exposure and was based on effects described in our previous publication.^{20,31} After incubation for 3 days, gene expression and cytokine levels were assessed. Details on quantitative RT-PCR are provided in the [Methods](#) section in this article's Online Repository.

Cytokine assessment

Cytokine concentrations were measured with the Human Cytokine Multiplex Assay Kit (Bio-Rad, Munich, Germany), according to the manufacturer's instructions. The lower limits of detection were 1.8 pg/mL (IL-5), 0.5 pg/mL (IL-6), 3.0 pg/mL (TNF- α), 0.9 pg/mL (IL-10), 2.1 pg/mL (IL-13), 1.3 pg/mL (IFN- γ), 0.5 pg/mL (IL-12), 1.0 pg/mL (GM-CSF), and 0.2 pg/mL (IL-17). Nondetectable cytokine concentrations were assigned a value of 0.01 for inclusion in the analysis.

Statistical analysis

All SNPs were tested for deviation from HWE by using the χ^2 test. LD between all SNPs was calculated by using R^2 . The R^2 threshold was set to 0.80 to determine tagging SNPs, each representing 1 LD block. Genetic data were analyzed with the χ^2 test (2 groups) or the Mantel-Haenszel test for trend (3 groups). Data of cytokine concentrations and gene expression, which were not normally distributed, were analyzed with the Wilcoxon test (2 groups) or the Kruskal-Wallis rank test (3 groups) and reported as medians (25%-75% interquartile ranges). Data were also reported stratified for maternal atopy. Diplo-type frequencies were estimated by using a combination of homozygous carriers of the selected variations. We did not adjust our data for multiple testing. Statistical significance was defined as a P value of less than .05. Data analysis was performed with SAS 9.2 software (SAS Institute, Cary, NC).

RESULTS

We assessed the genotype of 8 genetic variations in the *IL10* gene ([Table I](#)) with a genotyping success rate of greater than 90%. On the basis of LD analyses, 4 major LD blocks were identified ([Fig 1](#)), each represented by a tagging SNP. Two tagging SNPs (rs1800890 and rs1878672) slightly deviated from HWE; however, they showed similar allele frequencies in comparison to the HapMap reference population Centre d'Etude du Polymorphisme Humain. In the following we focused on reporting immunologic data that were differentially regulated in homozygous SNP carriers of various *IL10* polymorphisms reflecting a clear and consistent pattern; single results of particular SNPs were not reported in detail.

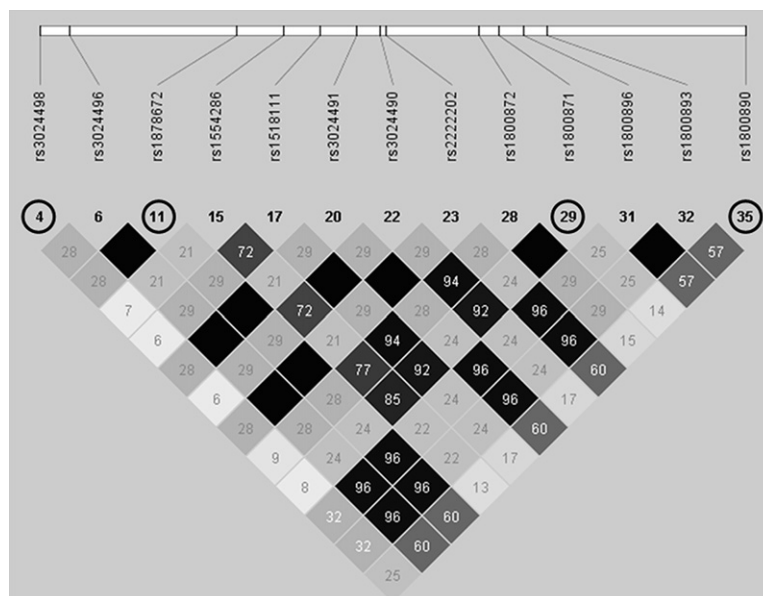


FIG 1. LD (R^2) plots for 13 frequent polymorphisms within the American (CEU) and European (TSI) population registered in the HapMap project (minor allele frequency >0.1 in both populations). All SNPs were located from the proximal promoter (-4000 bp) to the 3' untranslated region of *IL10*. Blocks of tagging SNPs were defined by R^2 values of greater than 0.80. Shades in LD plot (Haploview): white ($R^2 = 0$), gray ($0 < R^2 < 1$), and black ($R^2 = 1$). Tagging SNPs are marked with circles. The numbers describe the location of the genetic variations in this *IL10* region; in total, the region comprises 35 genetic variations.

TABLE I. Biological characteristics of the analyzed genetic variants of *IL10*

SNP/LD block	SNP	Relative position (bp)*	Alleles	Location	Δ AA	Δ TF	MAF
Distal promoter SNP 1	rs79309463	-7616	AGG/-	Promoter			0.21
Distal promoter SNP 2	rs10494879	-6365	C/G	Promoter			0.36
Block 1	rs1800890	-3526	A/T	Promoter	-	-	0.32
Block 2	rs1800871	-795	G/A	Promoter	-	+	0.25
Block 3	rs1800893	-1328	C/T	Promoter	-	+	0.44
	rs1878672 (tagging SNP)	2127	G/C	Intron	-	+	0.44
	rs3024496	3976	A/G	3'UTR	-	+	0.44
Block 4	rs3024498	4311	T/C	3'UTR	-	+	0.24

LD blocks are represented by 1 tagging SNP ($R^2 > 0.80$).

Δ AA, Predicted result of amino acid change in protein domain based on FastSNP analyses; Δ TF, predicted result of transcription factor binding site change based on FastSNP analyses; MAF, minor allele frequency within our study population; UTR, untranslated region.

*Relative position based on SNPper (CHIP Bioinformatic Tools).

***IL10* SNPs were associated with downregulated Treg cell-associated genes but not with *IL10* mRNA and protein levels**

We investigated the expression of the Treg cell-associated genes forkhead box protein P3 (*FOXP3*), lymphocyte activation gene 3 (*LAG3*), and glucocorticoid-induced TNF receptor (*GITR*) in CBMCs, genes that are highly correlated with each other. In carriers of genetic variants from all 4 LD blocks and 1 distal promoter SNP (rs79309463), at least 1 of the 3 investigated Treg cell-associated genes was downregulated compared with the wild-type (Table II; for raw data, see Table E1 in this article's Online Repository at www.jacionline.org). For carriers of the rs1800871 SNP (block 2), a significant downregulation of *FOXP3* and upregulation of *GITR* and *LAG3* was shown. *FOXP3* currently represents the most specific marker for natural Treg cells, and SNPs from 3 blocks (blocks 2, 3, and 4) showed decreased *FOXP3* mRNA expression.

Assessing *IL10* protein secretion and mRNA expression, carriers of the investigated SNPs did not show any significant differences in *IL10* levels apart from 2 SNPs. For homozygous carriers of deletion rs79309463, *IL10* protein but not mRNA levels were decreased before stimulation ($P = .03$), although at very low levels; for carriers of rs3024496 SNP (block 3), *IL10* protein and mRNA levels were increased after Der p 1 stimulation ($P = .05$ for both, data not shown).

Genetic variants in *IL10* were associated with *IL5* and *IFN-γ* cytokine secretion

Homozygous carriers of all SNPs except rs1800871 (block 2) showed a significant downregulation of the T_H2 cytokine *IL5* (for an overview, see Table II; for raw data, see Table E2 in this article's Online Repository at www.jacionline.org). In contrast to the consistent association with *IL5*, for *IL13* as another

TABLE II. Influence of genetic variants of *IL-10* on IL-5, IFN- γ , TNF- α , and GM-CSF cytokine secretion and gene expression of Treg-associated genes

LD block/SNP	IL-5		IFN- γ		TNF- α		GM-CSF		Treg cell marker genes	
rs79309463	↓	U* LpA*† Der p 1†		ND	↓	U* LpA† Ppg*† Der p 1*† Der p 1 + LpA†	↓	PHA* LpA† Der p 1*† Der p 1 + LpA†	↓	LAG3 U LpA† Ppg U*
rs10494879	↓	LpA Der p 1*†	↑	U*	↓	LpA*† Ppg*† Der p 1† Der p 1 + LpA*†	↓	PHA Der p 1† Der p 1 + LpA*†		ND
Block 1 rs1800890	↓	Der p 1*†	↑	U	↑	U* Ppg†		ND	↓	GITR U*
Block 2 rs1800871		ND		ND	↓	ND		ND	↓	FOXP3 (fd) LAG3 GITR Ppg
Block 3 rs1878672	↓	LpA* Der p 1*	↑	Der p 1 + LpA*	↓	LpA† Ppg*† Der p 1*† Der p 1 + LpA*	↓	Der p 1*†	↓	GITR (fd) Der p 1
Block 3 rs1800893	↓	LpA* Ppg* Der p 1* Der p 1 + LpA*	↑	Der p 1 + LpA*	↓	LpA† Ppg* Der p 1*† Der p 1 + LpA†		ND	↓	LAG3 Der p 1
Block 3 rs3024496	↓	LpA* Ppg Der p 1* Der p 1 + LpA	↑	Der p 1 + LpA	↓	LpA*† Ppg*† Der p 1*† Der p 1 + LpA*	↓	Der p 1	↓	FOXP3 U GITR U* (fd) Ppg* LAG3 U
Block 4 rs3024498	↓	LpA* Der p 1*†		ND	↓	LpA*† Ppg* Der p 1*† Der p 1 + LpA†	↓	PHA† LpA*† Der p 1* Der p 1 + LpA*†	↓	FOXP3 Ppg* GITR Ppg LAG3 Ppg*

Frequencies of single SNPs were variable depending on minor allele frequency (total n = 200).

†, Secretion/expression upregulated in homozygous carriers of the minor allele; ↓, secretion/expression downregulated in homozygous carriers of the minor allele; (fd), gene expression as fold difference; ND, no difference; U, unstimulated.

* $P \leq .05$, all other presented results are $P \leq .1$; P values are from the Kruskal-Wallis test.

†Highest/lowest secretion or gene expression in carriers with increasing number of the minor allele (SNP-heterozygous carrier-wild-type).

important mediator of allergic inflammation (T_H2), a significant reduction was only detected for the distal promoter SNP rs10494879 after Der p 1 stimulation ($P = .03$, data not shown).

Levels of the T_H1 cytokine IFN- γ were upregulated in homozygous carriers of SNPs from LD blocks 1 and 3 and the promoter SNP rs10494879 (Table II). However, the highest secretion was detected for heterozygous carriers of the SNPs. Concentrations of IL-12, another T_H1 cytokine, were not significantly different in the investigated *IL10* SNPs.

There was no consistently different pattern for the T_H17 marker cytokine IL-17 in carriers of the different *IL10* variants. Yet levels of the cytokine were significantly upregulated in carriers of the SNPs rs79309463 and rs1800890 (block 1) without stimulation ($P = .004/.01$, data not shown).

Downregulation of proinflammatory cytokines TNF- α and GM-CSF in carriers of *IL10* SNPs

Secretion of the proinflammatory cytokines TNF- α and GM-CSF was reduced in carriers of the distal promoter SNPs and LD blocks 3 and 4 (Table II; for raw data, see Table E2). Carriers of the rs1800890 SNP (block 1) showed higher secretion of TNF- α at baseline and lower secretion after Ppg

stimulation. Of note, independent of genotype, TNF- α and GM-CSF levels were highly correlated within all stimulation conditions. Concentrations of the proinflammatory cytokine IL-6 were not significantly different in carriers of the investigated *IL10* genotypes.

Maternal atopy had a minor influence on the immune response of *IL10* SNP carriers

Because we previously described an effect of maternal atopy on T-cell immune responses early in life,^{20,32} we performed analysis stratified for maternal atopy (see Table E3 in this article's Online Repository at www.jacionline.org). Dependent on the *IL10* genotype, IL-5 (see Table E2) and IL-13 (see Table E4 in this article's Online Repository at www.jacionline.org) secretion was primarily decreased in CBMCs of nonatopic mothers.

The effect of increased IFN- γ secretion was primarily observed in neonates of atopic mothers (see Table E3). For the SNP rs1878672 (block 3), *FOXP3* expression was higher after Der p 1 stimulation without maternal atopy but lower with maternal atopy. After LpA stimulation, carriers of the rs1800871 SNP (block 2) from nonatopic mothers showed reduced expression of *FOXP3*, whereas expression was increased with maternal

TABLE III. Effect of *IL10* SNPs on different clinical outcomes

SNP/LD block	Outcome		WT, % (n)	HT, % (n)	SNP, % (n)	P value (MH)
rs79309463	Wheeze	0	60 (63)	69 (31)	30 (3)	.07
		1	40 (42)	31 (14)	70 (7)	
	AD/wheeze	0	45 (47)	55 (24)	10 (1)	.04
		1	55 (58)	45 (20)	90 (9)	
rs10494879	AD/wheeze	0	47 (31)	50 (33)	23 (5)	.03
		1	53 (35)	50 (33)	77 (17)	
Block 1 rs1800890	AD/wheeze	0	47 (35)	51 (30)	24 (5)	.04
		1	53 (39)	49 (29)	76 (16)	
	AD	0	72 (53)	75 (44)	52 (11)	.07
		1	28 (21)	25 (15)	48 (10)	
Block 3 rs1878672	AD/wheeze	0	55 (30)	47 (30)	32 (12)	.04
		1	45 (25)	53 (34)	68 (26)	
Block 3 rs1800893	AD/wheeze	0	54 (29)	46 (30)	29 (10)	.02
		1	46 (25)	54 (35)	71 (25)	
Block 4 rs3024498	Wheeze	0	61 (62)	69 (31)	29 (4)	.02
		1	39 (39)	31 (14)	71 (10)	
	AD/wheeze	0	45 (45)	56 (25)	14 (2)	.03
		1	55 (55)	44 (20)	86 (12)	

0, Negative for respective outcome; 1, positive for respective outcome; AD, any symptoms of AD in the first 3 years of life; AD/wheeze, symptoms of AD, wheeze, or both in the first 3 years of life; HT, heterozygous carrier of the SNP; % (n), Percentage of children with respective genotype and outcome (number of cases); P value (MH), P value of Mantel-Haenszel test; wheeze, any wheezy symptoms in the first 3 years of life; WT, wild-type.

TABLE IV. SNP diplotypes of the genetic variants of *IL10* associated with outcome at age 3 years

Diplotype	SNP 1	SNP 2	SNP 3	SNP 4	SNP 5	SNP 6	SNP pattern		Wheeze		AD		AD/wheeze	
							N	Percent	n/N	Percent	n/N	Percent	n/N	Percent
0	—	—	—	—	—	—	125	76.7	43/110	39.1	32/109	29.4	57/109	52.3
1	—	—	—	x	x	—	11	6.8	3/10	30.0	3/10	30.0	5/10	50.0
2	—	x	x	x	x	—	10	6.1	2/9	22.2	5/9	55.6	6/9	66.7
3	x	x	x	x	x	x	10	6.1	7/10	70.0	5/10	50.0	9/10	90.0

AD, Any symptoms of AD in the first 3 years of life; AD/wheeze, symptoms of AD, wheeze, or both in the first 3 years of life; SNP 1, distal promoter SNP rs79309463 (deletion); SNP 2, distal promoter SNP rs10494879; SNP 3, rs1800890 (block 1); SNP 4, rs1878672 (block 3); SNP 5, rs1800893 (block 3); SNP 6, rs3024498 (Block 4); wheeze, any wheezy symptoms in the first 3 years of life; x, homozygous carrier of the respective SNP/deletion.

atopy (see Table E3). This diametric effect on expression of Treg cell-associated genes was already observed for TLR2 SNPs, depending on maternal atopy.³²

Effect of genetic *IL10* variants on clinical outcomes

Clinical outcomes regarding atopy, food allergy, or wheeze were assessed at 3 years of age, with a follow-up rate of 88%. Symptoms of AD were present in 29.5% of the children, whereas 37.5% showed wheezy symptoms within the first 3 years of life (see Table E5 in this article's Online Repository at www.jacionline.org). Carriers of the SNPs showed no association with food allergy. Having the *IL10* deletion rs79309463 or the SNP rs3024498 (block 4) presented as a risk factor for wheeze ($P = .07/.02$, Table III; see Table E6 in this article's Online Repository at www.jacionline.org), and homozygous carriers of the rs1800890 SNP (block 1) showed an increased risk for AD ($P = .07$, Table III). In parallel, symptoms of AD at age 3 years were associated with lower IL-5, TNF- α , and GM-CSF protein levels after primarily LpA stimulation and significantly lower *IL10* mRNA expression after innate stimulation (LpA, $P = .02$; Ppg, $P = .006$) in CBMCs independent of the genotype (see Table E7 in this article's Online Repository at www.jacionline.org). Opposite to the effects of Table II, showing less IL-5 in the presence of the *IL10* SNPs, wheeze was associated with higher IL-5 levels (see Table E7).

A higher risk for symptoms of AD, wheeze, or both was detected for homozygous carriers of the 2 distal promoter SNPs and the SNPs from LD blocks 1, 3, and 4 (all $P \leq .04$, Table III). In comparison with the tagging SNP from block 3 (rs1878672) and rs1800893, rs3024496 (block 3) was not significantly associated with an increased risk for symptoms of AD, wheeze, or both; however, it showed a trend ($P = .11$, data not shown). Although we observed an association of 6 SNPs with AD, wheeze, or symptoms of AD, wheeze, or both on the single-SNP level, no association of the respective *IL10* haplotype containing all 6 minor alleles with the observed outcomes was detected (data not shown).

SNP diplotypes

Table IV depicts the most frequent diplotypes of the 6 genetic variants that were associated with wheeze or AD at age 3 years (from Table III). Homozygous carriers of the SNPs rs1878672 and rs1800893 (block 3; diplotype 1) showed a similar prevalence of AD, wheeze, and symptoms of AD, wheeze, or both compared with children having none of the 6 SNPs (Table IV, diplotype 0). Homozygous carriers of these 2 SNPs from block 3 in addition to the SNPs rs10494879 (distal promoter SNP 2) and rs1800890 (block 1) (diplotype 2) showed an increase in AD prevalence from 29.4% (diplotype 0) to 55.6% (diplotype 2). In homozygous carriers of the 4 SNPs (diplotype 2), IL-5 (Der p 1) and IFN- γ (LpA and Der p 1) levels were decreased, whereas GM-CSF

secretion was increased at the baseline level (see Table E8 in this article's Online Repository at www.jacionline.org). Homozygous carriers of all 6 SNPs (diplotype 3) showed a higher AD prevalence and increased wheeze from 39.1% (diplotype 0) to 70.0% (diplotype 3, Table IV). Carriers of all 6 SNPs (diplotype 3) showed lower IL-5, TNF- α , and GM-CSF secretion (see Table E8).

DISCUSSION

In this study the effect of genetic variation in the *IL10* gene on secretion of T_H1/T_H2 lineage and proinflammatory cytokines and expression of Treg cells was assessed in cord blood. Additionally, the potential role of *IL10* SNPs on the development of immune-mediated diseases, such as AD or wheeze, until the age of 3 years was investigated. We detected a distinct pattern of T-cell lineage fate in carriers of *IL10* polymorphisms in cord blood because they were primarily associated with decreased expression of Treg cell marker genes and TNF- α and GM-CSF secretion and in parallel partially increased IFN- γ concentrations. Three of 4 *IL10* LD blocks and both distal promoter SNPs presented as determinants for wheeze, AD, or symptoms of wheeze, AD, or both at age 3 years. We have seen a consistent pattern independent of the SNP blocks, and thus we believe that these effects of different blocks are relevant.

We observed decreased mRNA expression of Treg cell marker genes (*FOXP3*, *LAG3*, and *GITR*) in carriers of the *IL10* SNPs. Reduced Treg cell numbers and potentially subsequently changed balance in immune regulation in SNP carriers might be in line with an increased risk for wheeze. Borrego et al³³ described diminished *FOXP3* mRNA expression and reduced CD4⁺CD25^{high} cell numbers for wheezy children at the age of 8 to 20 months. For adults with AD, however, normal or increased Treg cell numbers were reported compared with those seen in healthy control subjects,^{34,35} whereas we observed a reduced expression of Treg cell markers and the suppressive cytokine IL-10 in children with AD at age 3 years.

The assessment of Treg cell-associated markers by mRNA might be a first indication for Treg cell modulation. Measuring CD4⁺CD25⁺FOXP3⁺ cells would enhance specificity for Treg cells, but this was not feasible in all subjects of this birth cohort study, which assessed a wide range of immune parameters in parallel. Differences in Treg cell regulation within the aforementioned 2 studies and our study might potentially be attributable to different ages that cannot be compared directly and differences in assessed Treg cell markers, respectively.

Moreover, in carriers of the *IL10* SNPs, levels of the T_H2 cytokine IL-5 and the proinflammatory cytokines TNF- α and GM-CSF were significantly decreased in homozygous carriers of the SNPs. In parallel, carriers of 5 SNPs showed increased IFN- γ (T_H1) secretion, although IL-10 was originally discovered as cytokine synthesis inhibitory factor,⁷ which is capable of suppressing the T_H1 response.³⁶ Although *IL10* is mainly expressed by T_H2 and Treg cells, polymorphisms in the *IL10* gene seem to have an effect on the T_H1 lineage because IFN- γ secretion was affected. However, IFN- γ results have to be evaluated carefully and need to be reconfirmed in further studies because effects were primarily driven by heterozygous carriers and cytokines were assessed in bulk culture supernatants; consequently, the origin of the secreting cell cannot be ascribed to T_H1 cells only. Interestingly, we observed significantly increased IFN- γ

secretion in carriers of 3 single *IL10* SNPs, both unstimulated and after Der p 1 plus LpA stimulation, but IFN- γ levels were decreased under the same *in vitro* conditions in children with diplotype 2, carrying a combination of these *IL10* SNPs. Additionally, children with diplotype 2 showed a higher prevalence of AD. This shift in IFN- γ toward decreased levels in children with diplotype 2 could, for instance, be mediated by antigen-presenting cells, which strongly produce prostaglandin E₂ in patients with AD; prostaglandin E₂ is known to be able to modulate T-cell responses and especially decrease IFN- γ production by T cells.³⁷

This difference between single SNPs and diplotype might be explained by the number of subjects and a heterozygous effect.

Because TNF- α , GM-CSF, and IL-5 are 3 important mediators involved in allergic inflammation and a decrease in these cytokines parallel to an increase in IFN- γ levels was observed, this might point to an atopy-protective state of immune development already in cord blood.

We observed more prominent effects on IL-5 secretion after LpA compared with Ppg stimulation, which might be explained by a stronger effect of TLR4 in comparison with TLR2/NOD2 stimulation. Previously, we observed the strongest effects on IL-5 secretion after LpA stimulation.³⁸ Effects on IL-5 seem to be mainly mediated through TLR4 stimulation.³⁹ The reduction we described for IL-5 and IL-13 levels in CBMCs of nonatopic mothers would correspond to a predisposition toward a lower risk of later allergies.

Although we observed this shift from T_H2 toward T_H1 in the cytokine profile and reduced proinflammatory cytokine levels in newborn *IL10* SNP carriers, several of these *IL10* SNPs presented as risk factors for AD or wheeze in the follow-up analysis at age 3 years. Therefore polymorphisms in *IL10* seem to have an effect on early immune maturation before manifestation of clinical disease, favoring an atopy-prone immune development for AD. The predictive power for the children to have allergic diseases later in life would be mainly based on AD but not wheeze.⁴⁰

In contrast to our hypothesis, T_H2 cytokine levels were decreased and IFN- γ (T_H1) levels were increased in carriers of the *IL10* SNPs, who are prone to having AD or wheeze at the age of 3 years. One possible explanation for this could be that Treg cells, which were decreased in *IL10* SNP carriers, play a more fundamental role at this stage of early immune development compared with T_H1/T_H2 cytokine lineages.

Hee et al⁴¹ proposed *IL10* to be controlled at the transcriptional level, most likely by regulatory sequences present in the promoter region of the *IL10* gene, whereas their binding might be influenced by polymorphisms in these sites, affecting IL-10 production. In this study carriers of the SNPs, of which 5 were located in the promoter region, showed no significant changes in IL-10 mRNA levels and protein secretion. In line with our findings, Rees et al⁴² reported no consistent effect of the IL-10 genotype on IL-10 production. Moreover, Hayden et al⁴³ did not observe an association between *IL10* promoter SNPs and IL-10 production in house dust mite-stimulated PBMCs of 11-year-old children, yet they observed an association of *IL10* SNPs with T_H2 cytokine levels, indicating a pivotal role for IL-10 in the control of T_H2 cytokine secretion. Although *IL10* SNPs were associated with increased T_H2 levels in their study, we observed a decrease in IL-5 but not IL-13 levels for carriers of most of the investigated *IL10* SNPs. Potential differences might be due to the assessment at different times of immune maturation and thus different influences over time.

Intrauterine Treg cell development might already be affected in carriers of *IL10* polymorphisms. For example, one could imagine that binding of a transcription factor, such as activator protein 1, which is both relevant for activation of the IL-10 promoter and also for Treg cell regulation,^{44,45} might be modulated. However, the exact underlying mechanism needs to be determined.

To date, conflicting results regarding *IL10* SNPs and their association with asthma or atopy were reported. In our study the majority of *IL10* SNPs presented as risk factors for AD, wheeze, or symptoms of AD, wheeze, or both. Bossé et al¹³ observed an association with adult asthma in the Canadian Saguenay-Lac-Saint-Jean study population for 5 *IL10* SNPs, including rs1800871, which we assessed, whereas we did not find an association with any outcome at age 3 years. In the Childhood Asthma Management Program study population and in Costa Rican children, homozygous carriers of the minor allele rs3024496 were reported to have augmented levels of IgE and increased risk of occurrence and frequency of asthma at high levels of dust mite exposure.¹² In this study population we found a higher prevalence of AD, wheeze, or both for homozygous carriers of 2 SNPs from LD block 3, including SNP rs3024496.

Moreover, the minor allele of rs3024498 was described as a risk allele for childhood asthma in the Canadian Asthma Primary Prevention Study (CAPPS) study population and presented as a risk factor for wheeze and AD in our study, whereas the same allele was observed to be protective in children of the Study of Asthma Genes and the Environment cohort, and no association with asthma was observed within the Saguenay-Lac-Saint-Jean population and a German asthma family study.¹³ Although no association with AD was found for several *IL10* polymorphisms,⁴⁶ Sohn et al⁴⁷ showed an association for rs1800871 and rs1800872 with AD in children. In our study we did not find any association for carriers of the rs180871 SNP with the development of atopic diseases until age 3 years. It is interesting that the *IL10* SNPs presented as risk factors for both AD and wheeze, 2 potentially distinct diseases. Conflicting results about the association of polymorphisms with a disease outcome might result from differences in time of analysis, different assessment of the clinical phenotype, or failure to model gene-environment interactions adequately.¹²

It needs to be examined in the further follow-up of this and other studies whether these immune phenotypes result in asthma, which cannot be diagnosed by using objective parameters at age 3 years, or whether these children might be protected.

Because carriers of 6 *IL10* SNPs were associated with clinical outcomes at age 3 years, one could speculate that there exists a high-risk haplotype. However, carriers of the haplotype containing all 6 minor alleles associated with AD, wheeze, or symptoms of AD, wheeze, or both for carriers of the single SNPs were not associated with these outcomes. This might be explained by the higher number of heterozygous SNP carriers in the haplotype analysis, of which the majority showed a lower prevalence of wheeze and AD than homozygous SNP carriers.

The diplotype analysis showed that the distal promoter SNPs rs10494879 and/or rs1800890 (block 1) might be involved in the development of AD and that the SNP rs3024498 (block 4), the deletion rs79309463, or both might be involved in the development of wheeze in childhood. However, these 2 homozygous SNP/deletion genotype combinations alone did not occur within our study population, and thus their single effects cannot be disentangled. Additionally, prevalences of both SNPs are low, and therefore data need to be interpreted with caution.

Although impaired IFN- γ secretion at 3 months was associated with increased risk of recurrent wheeze during the first year,⁴⁸ no association between IFN- γ levels in cord blood and wheeze at age 1 year was found by Guerra et al⁴⁸ and Ly et al⁴⁹ and within our study for wheeze up to 3 years of age. Additionally, there was no association of IFN- γ levels and AD within the first 3 years of life.

We performed a stratified analysis for maternal atopy because it was shown to be relevant for Treg cell numbers and function.²⁰ Additionally, an influence of TLR polymorphisms on neonatal Treg cells was shown by our group, depending on the maternal atopy status.³² For the investigated *IL10* polymorphisms, stratifying for maternal atopy partly affected the observed cytokine secretion or Treg cell marker gene expression. The effect of increased IFN- γ secretion by SNP carriers was primarily influenced by atopic mothers, whereas we previously reported lower IFN- γ levels for CBMCs of atopic mothers, not taking the genotype into account.²⁰ This might point to an immunomodulatory effect through maternal atopy; however, the mechanisms are still not understood. An important point that needs to be considered is that results were not adjusted for multiple testing. It did not seem adequate for this study because the measurement of immunologic data in relation to the *IL10* SNPs was exploratory, the immunologic data were highly correlated, and the focus in this article was not on the SNP analysis *per se*. Consequently, the results require further replication in other studies.

However, we believe that the strength of this study is a detailed investigation of the immune system in relation to the *IL10* genotypes at the earliest possible time point, namely in cord blood. Moreover, we observed an effect on wheeze and atopy during the first 3 years. Finally, we will be able to follow these children to precisely assess atopic phenotypes until school age, including wheeze during later childhood and childhood asthma.

We thank the families for their participation in the study and midwives and doctors of the gynecology department for taking the cord blood samples. We thank Isolde Schleich for excellent technical assistance and Martin Depner for help in genotyping issues.

Clinical implications: These data support a critical role of *IL10* polymorphisms for early immune maturation and potentially for the development of AD and wheeze in childhood.

REFERENCES

- Mege JL, Meghari S, Honstetter A, Capo C, Raoult D. The two faces of interleukin 10 in human infectious diseases. *Lancet Infect Dis* 2006;6:557-69.
- O'Garra A, Vieira P. T(H)1 cells control themselves by producing interleukin-10. *Nat Rev Immunol* 2007;7:425-8.
- Taylor A, Verhagen J, Blaser K, Akdis M, Akdis CA. Mechanisms of immune suppression by interleukin-10 and transforming growth factor-beta: the role of T regulatory cells. *Immunology* 2006;117:433-42.
- Zhu J, Paul WE. Heterogeneity and plasticity of T helper cells. *Cell Res* 2010;20:4-12.
- Roncarolo MG, Gregori S, Battaglia M, Bacchetta R, Fleischhauer K, Levings MK. Interleukin-10-secreting type 1 regulatory T cells in rodents and humans. *Immunol Rev* 2006;212:28-50.
- Gruetz G. New insights into the molecular mechanism of interleukin-10-mediated immunosuppression. *J Leukoc Biol* 2005;77:3-15.
- Fiorentino DF, Zlotnik A, Mosmann TR, Howard M, O'Garra A. IL-10 inhibits cytokine production by activated macrophages. *J Immunol* 1991;147:3815-22.
- Borish L, Aarons A, Rumbyrt J, Cvietusa P, Negri J, Wenzel S. Interleukin-10 regulation in normal subjects and patients with asthma. *J Allergy Clin Immunol* 1996; 97:1288-96.
- Lyon H, Lange C, Lake S, Silverman EK, Randolph AG, Kwiatkowski D, et al. *IL10* gene polymorphisms are associated with asthma phenotypes in children. *Genet Epidemiol* 2004;26:155-65.

10. Corinti S, Albanesi C, la Sala A, Pastore S, Girolomoni G. Regulatory activity of autocrine IL-10 on dendritic cell functions. *J Immunol* 2001;166:4312-8.
11. Spits H, de Waal Malefyt R. Functional characterization of human IL-10. *Int Arch Allergy Immunol* 1992;99:8-15.
12. Hunninghake GM, Soto-Quiros ME, Lasky-Su J, Avila L, Ly NP, Liang C, et al. Dust mite exposure modifies the effect of functional IL10 polymorphisms on allergy and asthma exacerbations. *J Allergy Clin Immunol* 2008;122:93-8, e1-5.
13. Bossé Y, Lemire M, Poon AH, Daley D, He JQ, Sandford A, et al. Asthma and genes encoding components of the vitamin D pathway. *Respir Res* 2009;10:98.
14. Chatterjee R, Batra J, Kumar A, Mabalirajan U, Nahid S, Niphadkar PV, et al. Interleukin-10 promoter polymorphisms and atopic asthma in North Indians. *Clin Exp Allergy* 2005;35:914-9.
15. Gibson AW, Edberg JC, Wu J, Westendorp RG, Huizinga TW, Kimberly RP. Novel single nucleotide polymorphisms in the distal IL-10 promoter affect IL-10 production and enhance the risk of systemic lupus erythematosus. *J Immunol* 2001;166:3915-22.
16. Paradowska-Gorycka A, Trefler J, Maciejewska-Stelmach J, Lacki JK. Interleukin-10 gene promoter polymorphism in Polish rheumatoid arthritis patients. *Int J Immunogenet* 2010;37:225-31.
17. Asadullah K, Eskdale J, Wiese A, Gallagher G, Friedrich M, Sterry W. Interleukin-10 promoter polymorphism in psoriasis. *J Invest Dermatol* 2001;116:975-8.
18. Shin HD, Winkler C, Stephens JC, Bream J, Young H, Goedert JJ, et al. Genetic restriction of HIV-1 pathogenesis to AIDS by promoter alleles of IL10. *Proc Natl Acad Sci U S A* 2000;97:14467-72.
19. Schaub B, Campo M, He H, Perkins D, Gillman MW, Gold DR, et al. Neonatal immune responses to TLR2 stimulation: influence of maternal atopy on Foxp3 and IL-10 expression. *Respir Res* 2006;7:40.
20. Schaub B, Liu J, Hoppler S, Haug S, Sattler C, Lluís A, et al. Impairment of T-regulatory cells in cord blood of atopic mothers. *J Allergy Clin Immunol* 2008;121:1491-9, e1-13.
21. Kube D, Hua TD, von Bonin F, Schoof N, Zeynalova S, Kloss M, et al. Effect of interleukin-10 gene polymorphisms on clinical outcome of patients with aggressive non-Hodgkin's lymphoma: an exploratory study. *Clin Cancer Res* 2008;14:3777-84.
22. Kube D, Mormann M, Tomiuk J, Rieth H, Hua TD, Kremsner PG, et al. Simultaneous analysis of interleukin-10 gene microsatellites and single-nucleotide polymorphisms in parallel with tumour necrosis factor and interferon-gamma short tandem repeats by fluorescence-based polymerase chain reaction. *Genes Immun* 2003;4:459-68.
23. Rieth H, Mormann M, Luty AJ, Assouhou-Luty CA, Roupelieva M, Kremsner PG, et al. A three base pair gene variation within the distal 5'-flanking region of the interleukin-10 (IL-10) gene is related to the in vitro IL-10 production capacity of lipopolysaccharide-stimulated peripheral blood mononuclear cells. *Eur Cytokine Netw* 2004;15:153-8.
24. Wilk JB, Walter RE, Laramie JM, Gottlieb DJ, O'Connor GT. Framingham Heart Study genome-wide association: results for pulmonary function measures. *BMC Med Genet* 2007;8(suppl 1):S8.
25. Ding C, Cantor CR. A high-throughput gene expression analysis technique using competitive PCR and matrix-assisted laser desorption ionization time-of-flight MS. *Proc Natl Acad Sci U S A* 2003;100:3059-64.
26. Kormann MS, Carr D, Klopp N, Illig T, Leupold W, Fritzsche C, et al. G-Protein-coupled receptor polymorphisms are associated with asthma in a large German population. *Am J Respir Crit Care Med* 2005;171:1358-62.
27. Braun-Fahrlander C, Riedler J, Herz U, Eder W, Waser M, Grize L, et al. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002;347:869-77.
28. Ege MJ, Bieli C, Frei R, van Strien RT, Riedler J, Ublagger E, et al. Prenatal farm exposure is related to the expression of receptors of the innate immunity and to atopic sensitization in school-age children. *J Allergy Clin Immunol* 2006;117:817-23.
29. Willwerth BM, Schaub B, Tantisira KG, Gold DR, Palmer LJ, Litonjua AA, et al. Prenatal, perinatal, and heritable influences on cord blood immune responses. *Ann Allergy Asthma Immunol* 2006;96:445-53.
30. Contreras JP, Ly NP, Gold DR, He H, Wand M, Weiss ST, et al. Allergen-induced cytokine production, atopic disease, IgE, and wheeze in children. *J Allergy Clin Immunol* 2003;112:1072-7.
31. Schaub B, Liu J, Hoppler S, Schleich I, Huehn J, Olek S, et al. Maternal farm exposure modulates neonatal immune mechanisms through regulatory T cells. *J Allergy Clin Immunol* 2009;123:774-82, e5.
32. Liu J, Raedler D, Illi S, Klucker E, Turan E, von Mutius E, et al. TLR2 polymorphisms influence neonatal regulatory T cells depending on maternal atopy. *Allergy* 2011;66:1020-9.
33. Borrego LM, Arroz MJ, Videira P, Martins C, Guimaraes H, Nunes G, et al. Regulatory cells, cytokine pattern and clinical risk factors for asthma in infants and young children with recurrent wheeze. *Clin Exp Allergy* 2009;39:1160-9.
34. Hijnen D, Haeck I, van Kraats AA, Nijhuis E, de Bruin-Weller MS, Bruijnzeel-Koomen CA, et al. Cyclosporin A reduces CD4(+)CD25(+) regulatory T-cell numbers in patients with atopic dermatitis. *J Allergy Clin Immunol* 2009;124:856-8.
35. Vukmanovic-Stejić M, McQuaid A, Birch KE, Reed JR, Macgregor C, Rustin MH, et al. Relative impact of CD4+CD25+ regulatory T cells and tacrolimus on inhibition of T-cell proliferation in patients with atopic dermatitis. *Br J Dermatol* 2005;153:750-7.
36. Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. *Annu Rev Immunol* 2001;19:683-765.
37. Jung T, Moessner R, Dieckhoff K, Heidrich S, Neumann C. Mechanisms of deficient interferon-gamma production in atopic diseases. *Clin Exp Allergy* 1999;29:912-9.
38. Casaca VI, Illi S, Suttner K, Schleich I, Ballenberger N, Klucker E, et al. TBX21 and HLX1 polymorphisms influence cytokine secretion at birth. *PLoS One* 2012;7:e31069.
39. Dabbagh K, Dahl ME, Stepick-Biek P, Lewis DB. Toll-like receptor 4 is required for optimal development of Th2 immune responses: role of dendritic cells. *J Immunol* 2002;168:4524-30.
40. Spergel JM. Atopic march: link to upper airways. *Curr Opin Allergy Clin Immunol* 2005;5:17-21.
41. Hee CS, Gun SC, Naidu R, Gupta E, Somnath SD, Radhakrishnan AK. Comparison of single nucleotide polymorphisms in the human interleukin-10 gene promoter between rheumatoid arthritis patients and normal subjects in Malaysia. *Mod Rheumatol* 2007;17:429-35.
42. Rees LE, Wood NA, Gillespie KM, Lai KN, Gaston K, Mathieson PW. The interleukin-10-1082 G/A polymorphism: allele frequency in different populations and functional significance. *Cell Mol Life Sci* 2002;59:560-9.
43. Hayden CM, Zhang G, Judge PK, Khoo SK, Laing IA, Turner SW, et al. Regulatory role of IL10 genetic variations in determining allergen-induced T(H)2 cytokine responses in children. *J Allergy Clin Immunol* 2011;128:237-9, e8.
44. Kube D, Platzer C, von Knethen A, Straub H, Bohlen H, Hafner M, et al. Isolation of the human interleukin 10 promoter. Characterization of the promoter activity in Burkitt's lymphoma cell lines. *Cytokine* 1995;7:1-7.
45. Wu Y, Borde M, Heissmeyer V, Feuerer M, Lapan AD, Stroud JC, et al. FOXP3 controls regulatory T cell function through cooperation with NFAT. *Cell* 2006;126:375-87.
46. Kiyohara C, Tanaka K, Miyake Y. Genetic susceptibility to atopic dermatitis. *Allergol Int* 2008;57:39-56.
47. Sohn MH, Song JS, Kim KW, Kim ES, Kim KE, Lee JM. Association of interleukin-10 gene promoter polymorphism in children with atopic dermatitis. *J Pediatr* 2007;150:106-8.
48. Guerra S, Lohman IC, Halonen M, Martinez FD, Wright AL. Reduced interferon gamma production and soluble CD14 levels in early life predict recurrent wheezing by 1 year of age. *Am J Respir Crit Care Med* 2004;169:70-6.
49. Ly NP, Rifas-Shiman SL, Litonjua AA, Tzianabos AO, Schaub B, Ruiz-Perez B, et al. Cord blood cytokines and acute lower respiratory illnesses in the first year of life. *Pediatrics* 2007;119:e171-8.

Table E1: Gene expression of Forkhead-Box-Protein P3 (FOXP3), Glucocorticoid-induced TNFR-related protein (GITR) and Lymphocyte-activation gene 3 (LAG3) stratified for maternal atopy (raw data).

Forkhead box P3 (FOXP3)													
LD-Block/SNP	Genotype	CBMCs all				CBMCs of non-atopic mothers				CBMCs of atopic mothers			
		1.Q	Med	3.Q	p(KW)	1.Q	Med	3.Q	p(KW)	1.Q	Med	3.Q	p(KW)
rs79309436	Δ ct												
	WT	14.09	14.09	17.58		14.09	16.15	17.75		14.09	14.09	16.70	
	U	14.09	16.70	17.88	0.24	15.88	17.08	18.50	0.33	14.09	15.07	16.85	0.57
	SNP	14.09	16.30	16.85		14.09	16.30	16.85		14.09	16.30	18.60	
	WT	10.15	12.20	13.80		10.55	12.53	14.35		9.18	10.98	12.28	
	PHA	10.50	12.68	14.70	0.38	11.05	13.43	14.70	0.65	10.05	11.43	13.58	0.05
	SNP	10.95	13.28	15.75		9.80	10.95	14.05		12.50	15.75	16.50	
	WT	12.55	15.20	16.15		13.95	15.40	16.35		12.40	14.35	15.95	
	LpA	14.70	15.85	16.20	0.27	15.15	16.00	16.40	0.34	11.80	14.48	15.70	0.52
	SNP	14.90	15.98	17.08		15.00	16.10	17.20		14.80	15.88	16.95	
	WT	12.98	14.73	15.80		13.75	15.00	16.00		12.10	13.78	14.90	
	Ppg	14.10	15.38	16.60	0.18	14.20	15.40	16.65	0.56	12.70	15.00	15.80	0.20
	SNP	15.45	15.70	15.90		11.20	15.90	16.60		15.45	15.58	15.70	
	WT	12.48	14.40	16.45		13.00	14.95	17.30		11.60	13.20	15.90	
	D	12.70	14.60	16.80	0.59	12.70	15.50	16.80	0.99	12.70	13.90	15.90	0.21
	SNP	14.30	16.30	16.85		14.30	14.30	14.30		16.30	16.58	16.85	
rs10494879	Δ ct												
	WT	14.09	14.09	17.75		14.09	14.52	18.25		14.09	14.09	17.10	
	U	14.09	16.33	17.55	0.33	15.30	17.08	18.25	0.24	14.09	14.09	16.50	0.70
	SNP	14.09	16.30	17.15		14.09	16.30	17.10		14.09	16.30	17.20	
	WT	9.78	11.80	13.70		10.55	12.53	14.60		9.10	10.20	12.85	
	PHA	10.95	12.43	14.05	0.52	12.25	13.30	14.40	0.24	10.90	11.10	12.10	0.07
	SNP	10.00	12.43	14.85		8.80	10.95	14.05		12.50	15.00	15.75	
	WT	12.40	15.00	16.10		13.95	15.38	16.40		12.25	14.00	15.95	
	LpA	14.35	15.65	16.20	0.28	14.98	15.90	16.28	0.49	12.55	14.60	15.95	0.70
	SNP	14.80	16.15	16.95		15.00	16.60	17.00		13.18	15.48	16.55	
	WT	12.95	14.60	15.90		13.90	15.05	16.20		11.85	13.23	15.00	
	Ppg	13.93	14.93	15.78	0.25	14.20	15.30	16.00	0.60	12.70	14.75	15.70	0.31
	SNP	15.45	15.90	16.65		15.90	16.60	16.65		13.75	15.58	16.33	
	WT	11.75	13.78	17.00		13.20	14.45	17.55		11.20	11.80	14.95	
	D	14.20	15.60	16.20	0.66	11.95	15.60	16.20	0.59	14.60	15.35	16.60	0.10
	SNP	12.70	14.30	16.30		12.70	13.50	14.30		12.20	16.30	16.85	
rs1800890 Block1	Δ ct												
	WT	14.09	14.09	17.75	0.16	14.09	14.95	18.25	0.23	14.09	14.09	17.10	0.69
U	HT	14.09	16.70	17.40		15.70	17.05	18.35		14.09	15.07	16.70	

	PHA	SNP	14.09	16.30	17.15	0.70	14.09	16.30	17.10	0.35	14.09	16.30	17.20	0.02					
		WT	10.10	12.35	13.80		11.00	12.73	14.50		9.10	10.53	12.85						
		HT	10.90	12.40	14.05		10.70	13.30	14.70		10.90	11.08	12.10						
	LpA	SNP	10.38	12.48	14.85	0.13	8.80	10.95	14.05	0.67	12.50	15.00	15.75	0.16					
		WT	12.40	15.20	16.10		14.65	15.40	16.40		12.25	14.00	15.70						
		HT	14.70	15.80	16.20		14.95	15.85	16.20		14.30	15.20	16.48						
	Ppg	SNP	14.90	16.38	16.98	0.23	15.00	16.60	17.00	0.85	14.80	16.15	16.95	0.04					
		WT	12.95	14.80	15.85		14.40	15.30	16.10		11.50	12.95	15.00						
		HT	14.08	14.93	15.90		14.10	15.00	16.15		14.05	14.80	15.70						
	D	SNP	15.45	15.90	16.65	0.83	11.90	16.25	16.65	0.50	15.45	15.70	16.95	0.09					
		WT	11.75	13.85	17.00		13.20	15.15	17.55		11.20	11.80	14.95						
		HT	12.70	15.00	16.20		12.33	15.35	16.10		13.20	14.70	16.60						
			SNP	13.65	15.30	16.58				13.00	13.65	14.30							
rs1800871 Block 2	U	Δct				0.33				0.24				0.41					
		WT	14.09	16.15	17.40		14.09	16.35	17.40		14.09	14.09	17.40						
		HT	14.09	16.33	17.80		14.09	17.30	18.65		14.09	14.09	16.60						
	PHA	SNP	14.09	14.09	14.95	0.90	14.09	14.09	14.95	0.23	14.09	14.09	14.09	0.47					
		WT	10.13	12.40	14.00		10.13	12.68	14.00		10.05	11.60	14.30						
		HT	10.30	12.38	14.30		12.30	13.80	15.10		9.25	10.20	11.95						
	LpA	SNP	10.55	11.20	15.05	0.92	10.55	13.00	15.05	0.39	10.85	11.03	11.20	0.10					
		WT	13.40	15.40	16.25		14.30	15.55	16.35		12.98	15.00	16.20						
		HT	14.00	15.00	16.05		15.00	15.95	17.25		11.20	13.45	14.25						
	Ppg	SNP	12.40	14.80	16.10	0.80	13.95	14.80	16.10	0.30	12.40	14.20	16.00	0.32					
		WT	13.18	15.05	15.95		14.10	15.30	16.00		12.50	14.80	15.70						
		HT	13.80	14.70	15.90		14.68	15.83	16.73		11.43	13.10	14.80						
	D	SNP	13.50	13.90	15.00	0.53	13.13	13.90	16.28	0.02	13.50	14.25	15.00	0.41					
		WT	13.00	14.45	16.30		13.00	14.25	16.20		13.10	14.70	16.30						
		HT	11.70	15.60	17.20		15.60	17.10	17.70		10.85	11.75	14.95						
				SNP	13.00	13.50	14.20				12.48	13.25	13.85	14.60	14.60	14.60			
	PHA	fd				0.22				0.19				0.73					
		WT	6.21	17.69	51.10		7.09	18.96	48.62		4.59	14.37	55.78						
		HT	4.40	16.92	34.30		3.83	12.38	33.15		11.71	24.25	28.62						
	LpA	SNP	3.86	7.41	11.62	0.04	3.86	6.06	11.62	0.06	7.41	8.42	9.44	0.26					
		WT	1.61	2.91	4.59		1.87	3.14	4.59		1.24	2.87	4.44						
		HT	1.87	4.14	6.50		2.07	4.14	6.50		1.87	4.76	10.12						
	Ppg	SNP	0.27	1.11	3.22	0.02	1.10	1.11	1.32	0.02	0.27	1.75	3.22	0.23					
		WT	1.65	3.29	6.02		1.92	4.14	5.86		1.27	3.01	6.28						
HT		3.03	4.29	6.96	4.00		5.71	7.09	1.42		3.13	6.61							
D	SNP	1.15	1.38	1.87	0.79	1.21	1.57	2.44	0.11	0.53	1.02	1.50	0.51						
	WT	1.04	2.06	5.19		1.61	2.13	6.68		1.00	1.85	4.76							
	HT	0.62	1.54	5.24		0.47	1.19	1.62		0.62	5.06	9.44							
			SNP	1.50	1.68	2.13				1.59	1.90	3.27	0.70	0.70	0.70				
rs1878672		Δct																	

Block 3	U	WT	14.09	14.09	17.93		14.09	14.52	18.48		14.09	14.09	16.60	
		HT	14.09	16.50	17.40		14.75	16.90	17.40	0.71	14.09	15.04	17.15	0.50
		SNP	14.09	16.30	17.63	0.28	14.09	16.98	17.90		14.09	15.07	17.45	
	PHA	WT	10.20	12.40	13.80		11.40	12.90	15.05		9.25	10.53	12.85	
		HT	10.60	12.38	14.05		10.60	12.68	14.30	0.62	9.53	11.48	12.03	0.18
		SNP	10.20	12.45	14.70	0.94	9.30	12.60	14.20		10.95	12.45	15.00	
	LpA	WT	12.40	15.25	16.10		14.65	15.60	16.50		11.75	12.93	15.70	
		HT	14.33	15.53	16.15		14.80	15.75	16.15	0.88	14.00	14.48	15.95	0.38
		SNP	13.40	15.63	16.60	0.54	15.00	15.85	16.60		13.40	14.80	16.15	
	Ppg	WT	13.00	14.90	16.10		14.05	15.85	16.30		12.35	13.50	15.00	
		HT	13.93	14.80	15.78		14.20	15.05	16.00	0.80	11.50	14.40	14.80	0.17
		SNP	15.00	15.50	16.60	0.46	15.10	15.50	16.60		13.75	15.58	16.33	
	D	WT	11.80	14.13	16.30		13.40	14.70	17.60		11.03	11.75	14.78	
		HT	11.95	15.60	16.90		11.95	15.60	16.80	0.70	14.80	16.60	16.90	0.07
		SNP	13.05	14.45	16.25	0.72	13.00	14.30	16.20		13.10	14.60	16.30	
	PHA	fd												
		WT	4.00	11.71	30.91		3.22	6.26	27.86		9.44	19.87	30.91	
		HT	7.21	18.70	43.71	0.61	7.46	18.70	41.90	0.11	4.50	16.69	55.78	0.60
	LpA	SNP	5.46	14.82	42.22		10.21	32.31	41.51		3.11	8.81	61.35	
		WT	1.32	4.11	5.24		1.32	4.50	5.28		1.56	3.22	5.06	
		HT	1.77	3.14	4.84	0.79	1.87	2.94	4.92	0.67	1.68	3.36	4.76	0.84
	Ppg	SNP	1.46	2.65	4.25		1.46	2.46	4.25		1.61	2.83	3.14	
		WT	1.80	3.03	4.92		2.05	3.03	5.24		1.50	3.22	4.44	
		HT	2.15	4.14	6.50	0.75	2.83	4.14	6.50	0.92	0.87	3.82	6.91	0.96
	D	SNP	1.37	3.01	7.41		1.37	4.56	7.41		1.40	2.32	6.49	
		WT	1.03	1.96	4.89		1.03	1.62	2.13		2.73	5.06	8.42	
		HT	0.62	1.33	5.61	0.81	0.73	1.46	6.68	0.09	0.62	1.07	1.62	0.27
		SNP	1.43	2.37	3.85		2.62	3.61	4.00		0.28	1.85	3.70	
rs1800893	Block 3	Δct												
		WT	14.09	14.09	18.10		14.09	14.09	18.48		14.09	14.09	16.60	
		HT	14.09	16.20	17.40	0.49	14.42	16.55	17.40	0.76	14.09	14.09	16.70	0.75
	U	SNP	14.09	16.30	17.30		14.09	16.85	17.30		14.09	15.07	17.45	
		WT	10.20	12.65	14.00		11.40	12.90	15.05		9.35	10.53	12.95	
		HT	10.33	12.23	14.00	0.80	10.35	12.65	14.05	0.58	9.90	11.05	11.95	0.19
	PHA	SNP	10.58	12.40	14.85		9.80	12.35	14.05		10.95	12.45	15.00	
		WT	12.40	14.80	16.25		13.95	15.38	16.50		11.80	12.93	15.48	
		HT	14.25	15.40	16.15	0.52	14.70	15.55	16.15	0.46	12.25	14.35	15.95	0.40
	LpA	SNP	13.40	15.70	16.95		15.00	16.40	17.00		13.40	14.80	16.15	
		WT	13.05	14.60	16.10		13.75	15.85	16.30		11.85	13.50	15.00	
		HT	13.80	14.80	15.45	0.46	14.20	15.00	15.70	0.76	11.50	14.05	14.80	0.18
	Ppg	SNP	12.50	15.70	16.65		11.90	15.90	16.65		13.75	15.58	16.33	
		WT	11.88	13.78	16.90		13.00	14.20	17.60		10.85	11.75	14.95	
		HT	13.05	15.55	16.85	0.71	12.70	15.50	16.80	0.89	14.80	16.60	16.90	0.12

	PHA	SNP	13.10	14.45	16.20		13.00	14.30	16.20		13.10	14.60	16.30		
		WT	3.86	11.62	30.91		3.22	6.26	15.45		10.58	19.87	29.77		
		HT	7.34	20.07	47.73	0.29	7.46	21.11	45.25	0.10	4.59	18.24	50.21	0.66	
	LpA	SNP	5.37	13.69	39.94		6.96	19.55	39.10		3.11	8.81	61.35		
		WT	1.32	3.97	5.28		1.32	4.27	5.28		1.71	3.22	6.17		
		HT	1.68	3.14	4.89	0.41	1.37	2.73	5.24	0.36	1.68	3.58	4.89	0.70	
	Ppg	SNP	1.41	2.14	3.14		1.41	1.80	2.46		1.61	2.83	3.14		
		WT	1.80	3.03	4.76		1.87	3.01	4.92		1.50	3.22	4.72		
		HT	2.30	4.14	6.50	0.47	2.83	4.14	6.50	0.32	0.87	2.62	6.91	0.96	
	D	SNP	1.32	1.74	4.59		1.32	1.74	4.59		1.40	2.32	6.49		
		WT	1.27	2.13	4.82		1.03	1.68	2.13		4.76	5.06	9.44		
		HT	0.67	1.54	4.13	0.72	0.73	1.61	6.68	0.22	0.62	1.07	1.62	0.24	
	SNP	1.00	2.06	4.00		2.13	4.00	13.45		0.28	1.85	3.70			
rs3024496 Block 3	U	Δct													
		WT	14.09	14.09	17.43		14.09	14.09	18.40		14.09	14.09	15.34		
		HT	14.09	16.50	17.60	0.09	15.03	16.98	17.55	0.31	14.09	14.09	17.60	0.37	
	PHA	SNP	14.09	16.18	17.20		14.09	16.30	17.10		14.09	16.05	17.20		
		WT	10.20	12.20	13.60		11.40	12.80	15.05		9.25	10.85	12.85		
		HT	10.35	12.40	14.05	0.90	10.60	12.70	14.30	0.59	8.15	10.90	12.10	0.17	
	LpA	SNP	10.20	12.15	14.70		8.80	10.95	14.05		11.00	12.30	15.00		
		WT	12.05	14.65	16.00		13.95	15.35	16.40		11.20	12.40	15.70		
		HT	14.48	15.48	16.15	0.19	14.80	15.65	16.15	0.88	14.25	14.60	15.95	0.16	
	Ppg	SNP	12.98	15.35	16.40		12.40	15.60	16.60		13.40	15.25	16.15		
		WT	12.40	14.05	15.90		13.40	15.38	16.50		11.85	12.95	15.00		
		HT	13.95	14.83	15.78	0.45	14.20	15.10	16.00	0.98	12.95	14.75	14.80	0.15	
	D	SNP	12.50	15.45	16.60		11.90	15.50	16.60		14.05	15.45	15.70		
		WT	11.80	13.50	14.95		13.20	14.13	17.55		11.03	11.75	14.78		
		HT	11.95	15.40	16.90	0.61	11.95	15.60	16.80	0.73	13.20	14.80	16.90	0.11	
		SNP	13.05	14.45	16.25		12.85	13.65	15.25		13.15	15.25	16.45		
	rs3024498 Block 3	U	Δct												
			WT	14.09	14.42	17.58		14.09	16.35	17.75		14.09	14.09	16.90	
HT			14.09	16.13	17.35	0.48	14.09	16.90	18.35	0.81	14.09	16.00	16.50	0.49	
PHA		SNP	14.09	16.30	18.60		15.19	16.58	18.00		14.09	16.30	18.60		
		WT	10.15	12.10	13.60		10.55	12.65	14.05		9.10	10.90	12.10		
		HT	10.95	12.68	14.70	0.29	11.05	13.13	14.70	0.83	10.95	12.18	15.00	0.11	
LpA		SNP	10.95	12.50	14.35		10.38	12.50	14.20		12.15	12.50	15.75		
		WT	12.48	15.18	16.15		14.30	15.40	16.15		12.40	14.18	15.95		
		HT	14.95	15.90	16.40	0.23	15.00	15.98	16.50	0.37	14.43	15.15	15.93	0.76	
Ppg		SNP	14.70	15.00	16.95		15.00	15.85	17.20		13.13	14.75	15.88		
		WT	12.98	14.68	15.80		13.75	14.90	16.00		12.10	13.78	14.90		
		HT	15.00	15.70	16.65	0.04	15.00	15.58	16.65	0.35	14.75	15.75	16.38	0.13	
	SNP	13.53	15.48	15.80		13.35	15.70	16.25		13.53	15.23	15.58			

D	WT	11.95	14.13	16.30	0.50	13.00	14.45	17.30	0.83	11.60	13.20	15.90	0.34
	HT	13.20	15.55	16.80		13.45	15.55	16.50		13.20	15.20	17.20	
	SNP	14.30	15.45	16.85		14.30	15.80	17.30		13.40	15.45	16.58	
Glucocorticoid-induced TNFR-related protein (GITR)													
rs79309463	Δct				0.05				0.16				0.35
U	WT	14.28	14.28	17.35		14.28	16.40	17.65		14.28	14.28	16.15	
	HT	14.28	16.25	18.10		15.30	16.85	18.30		14.28	15.27	17.15	
	SNP	14.28	15.78	17.80	14.28	16.40	17.95	14.28	15.15	17.80			
PHA	WT	10.20	12.80	15.10	0.67	10.60	13.40	15.15	0.82	9.45	11.55	15.05	0.40
	HT	10.80	13.20	15.25		11.50	14.00	15.55		9.48	12.58	13.80	
	SNP	12.70	13.45	16.20		10.80	12.70	16.40		13.30	13.60	16.20	
LpA	WT	13.45	15.25	16.80	0.30	13.45	15.30	16.75	0.36	13.55	15.10	17.40	0.85
	HT	14.65	16.00	17.10		14.80	15.90	17.10		14.65	16.15	16.75	
	SNP	15.63	16.45	17.78		15.75	17.08	18.40		15.50	16.33	17.15	
Ppg	WT	12.70	15.00	15.95	0.30	13.10	14.85	15.75	0.32	12.30	15.20	16.50	0.64
	HT	14.03	15.50	16.10		14.10	15.55	16.00		12.95	15.50	16.70	
	SNP	14.50	15.00	15.85		11.50	15.85	18.00		14.50	14.75	15.00	
D	WT	12.00	14.10	16.50	0.79	12.00	15.50	16.70	0.99	12.00	12.45	16.20	0.76
	HT	12.60	15.40	16.20		12.60	15.40	16.20		12.60	15.70	17.20	
	SNP	14.80	14.90	15.50		15.50	15.50	15.50		14.80	14.85	14.90	
rs10494879	Δct				0.21				0.06				0.71
U	WT	14.28	14.28	17.35		14.28	15.75	17.45		14.28	14.28	17.10	
	HT	14.28	16.17	18.10		15.60	17.30	18.10		14.28	14.28	16.35	
	SNP	14.28	15.70	17.33	14.28	16.40	17.90	14.28	15.15	16.25			
PHA	WT	10.15	12.68	15.15	1.00	10.55	12.68	15.65	0.35	9.45	13.95	15.10	0.13
	HT	10.90	13.53	14.90		12.38	13.90	15.48		9.48	11.28	13.10	
	SNP	11.38	13.00	15.45		7.90	11.95	15.60		13.30	13.60	15.30	
LpA	WT	13.45	15.10	16.85	0.40	13.45	15.25	16.85	0.40	13.55	15.10	17.40	0.76
	HT	15.00	16.00	16.95		15.10	15.95	17.10		12.98	16.13	16.78	
	SNP	14.65	16.00	17.15		11.45	16.00	16.30		15.08	16.33	17.45	
Ppg	WT	12.30	14.70	16.00	0.25	13.10	14.65	15.45	0.18	12.30	15.20	16.50	0.93
	HT	13.95	15.30	15.90		14.23	15.28	15.98		12.95	15.33	15.50	
	SNP	14.65	15.45	16.20		14.65	15.93	16.20		14.75	15.03	16.03	
D	WT	12.15	13.90	16.40	0.53	12.50	15.50	17.00	0.77	11.73	12.38	14.80	0.15
	HT	13.30	16.00	16.35		11.60	15.80	16.20		16.20	16.20	18.20	
	SNP	14.80	14.90	15.20		12.60	14.05	15.50		14.80	14.90	15.20	
PHA	fd				0.36				0.47				0.06
	WT	2.46	9.66	28.46		2.91	8.37	19.23		0.70	13.75	28.46	
	HT	3.54	15.21	45.36		2.97	10.58	40.81		10.26	27.98	49.90	
LpA	SNP	2.65	4.15	37.41	0.48	2.93	13.00	83.34	0.69	1.93	3.03	3.61	0.45
	WT	1.32	2.46	4.86		1.78	2.73	5.10		0.95	1.50	2.93	
	HT	0.87	1.68	5.66		1.27	1.68	5.66		0.57	2.21	7.67	
	SNP	0.77	1.54	3.03		1.52	2.30	7.12		0.56	0.78	1.18	

Ppg	WT	1.13	3.95	7.46	0.12	2.12	4.44	7.46	0.12	0.57	3.95	5.21	0.89
	HT	2.30	3.52	6.96		2.42	4.68	7.04		1.80	2.49	3.86	
	SNP	0.77	1.52	3.25		0.97	1.63	3.25		0.59	1.08	4.27	
D	WT	1.31	3.02	4.86	0.33	0.93	1.62	3.86	0.52	3.01	4.40	6.92	0.09
	HT	0.86	2.88	8.53		0.97	4.14	8.88		0.84	0.87	7.73	
	SNP	0.65	1.27	1.87		1.87	2.54	3.21		0.53	0.65	1.27	
rs1800890	Δct												
Block 1	WT	14.28	14.28	17.35	0.03	14.28	16.08	17.48	0.08	14.28	14.28	16.63	0.51
	U	14.28	16.20	18.10		15.30	16.70	18.30		14.28	15.14	16.60	
	SNP	14.28	15.70	17.33		14.28	16.40	17.90		14.28	15.15	16.25	
PHA	WT	10.40	12.85	15.15	0.97	11.15	13.13	15.60	0.54	9.20	12.23	15.10	0.39
	HT	11.25	13.15	15.13		11.50	13.80	15.40		11.00	12.05	13.10	
	SNP	10.50	13.00	15.45		7.90	11.95	15.60		13.30	13.60	15.30	
LpA	WT	13.55	15.25	16.85	0.58	14.20	15.28	16.85	0.80	13.55	15.05	17.40	0.34
	HT	14.65	15.95	16.80		14.85	15.88	17.03		10.95	16.10	16.75	
	SNP	15.50	16.25	17.15		11.65	16.00	16.30		15.50	17.15	17.75	
Ppg	WT	13.10	14.85	16.00	0.53	13.20	14.78	15.75	0.71	11.90	15.15	16.50	0.76
	HT	14.05	15.30	15.90		13.95	15.25	15.90		14.55	15.33	15.50	
	SNP	14.50	15.43	16.20		11.50	15.85	16.20		14.50	15.00	17.00	
D	WT	12.38	14.05	16.40	0.56	12.60	15.50	17.00	0.39	11.73	12.38	14.80	0.28
	HT	12.60	15.80	16.20		12.10	15.60	16.10		15.20	16.20	16.20	
	SNP	11.25	14.85	15.20		7.70	11.60	15.50		14.80	14.85	14.90	
rs1800871	Δct												
Block 2	WT	14.28	15.85	17.60	0.54	14.28	16.40	17.95	0.53	14.28	14.28	16.35	0.63
	U	14.28	15.93	17.70		14.28	16.63	18.05		14.28	14.28	17.35	
	SNP	14.28	14.28	16.30		14.28	15.19	16.50		14.28	14.28	14.28	
PHA	WT	10.20	12.80	15.05	0.54	10.55	13.00	15.43	0.48	9.45	12.80	14.55	0.27
	HT	10.80	13.88	15.40		12.85	14.20	15.40		10.33	13.53	15.35	
	SNP	9.10	12.55	16.50		11.15	13.90	16.50		9.10	9.10	9.10	
LpA	WT	13.90	15.55	16.95	0.78	13.20	15.55	16.92	0.72	14.35	15.80	17.15	0.68
	HT	15.10	15.95	16.63		15.18	15.95	16.63		13.55	16.15	17.40	
	SNP	13.45	13.70	17.00		12.15	15.23	17.35		13.70	13.70	13.70	
Ppg	WT	12.70	15.00	16.00	0.61	13.83	14.93	16.00	0.65	12.50	15.05	15.50	0.83
	HT	14.50	15.25	15.90		14.70	15.30	15.75		12.95	15.25	16.70	
	SNP	13.65	14.83	16.20		13.20	14.65	15.90		14.45	15.48	16.50	
D	WT	12.30	15.00	16.20	0.10	12.50	15.40	16.20	0.07	12.30	14.85	16.20	0.98
	HT	15.00	16.05	17.20		15.80	16.10	17.20		10.90	14.55	18.20	
	SNP	12.00	13.80	14.00		11.08	13.00	15.30		13.80	13.80	13.80	
rs1878672	Δct												
Block 3	WT	14.28	14.28	16.90	0.17	14.28	15.15	17.45	0.20	14.28	14.28	16.15	0.68
	U	14.28	16.13	18.00		15.30	16.70	18.10		14.28	14.28	17.10	
	SNP	14.28	16.30	17.85		14.28	16.63	17.95		14.28	14.72	16.48	
	WT	10.40	13.03	15.60		10.88	13.03	16.20		10.15	13.95	15.10	

	PHA	HT	10.80	13.70	15.25	0.94	11.50	13.90	15.25	0.78	9.08	12.18	13.95	0.58
		SNP	10.80	13.10	15.10		9.35	12.75	15.35		11.00	13.30	14.55	
		WT	13.45	15.25	16.90		13.83	15.33	16.88		12.85	15.70	17.40	
	LpA	HT	14.35	15.80	16.75	0.82	14.80	15.80	16.95	0.83	13.95	15.55	16.42	0.61
		SNP	14.65	15.75	16.80		11.65	15.75	16.25		14.90	16.75	17.15	
		WT	14.10	15.15	16.10		13.10	14.70	15.75		14.78	15.68	16.55	
	Ppg	HT	13.83	14.93	15.90	0.48	13.95	15.00	15.90	0.58	12.30	14.05	15.35	0.37
		SNP	14.65	15.50	16.00		14.65	15.78	16.00		15.00	15.30	15.50	
		WT	12.00	13.95	16.20		12.50	15.00	16.60		11.18	12.63	15.00	
	D	HT	12.45	15.80	16.50	0.65	13.30	15.90	16.60	0.96	12.45	15.80	16.20	0.52
		SNP	12.50	15.05	16.20		12.60	15.50	16.20		12.40	14.90	16.20	
		fd												
	PHA	WT	2.46	8.37	17.52		2.63	7.30	13.78		0.57	13.75	17.52	0.64
		HT	2.79	13.07	42.22	0.39	3.48	11.51	42.22	0.21	1.90	24.67	39.20	
		SNP	2.93	7.21	48.50		4.50	12.08	72.58		1.93	3.61	28.46	
	LpA	WT	1.19	2.46	3.44		1.48	2.51	3.18		0.34	1.78	3.89	0.51
		HT	1.23	1.74	5.66	0.72	1.41	2.00	5.66	0.80	0.94	1.28	10.62	
		SNP	0.77	1.57	5.66		1.57	3.45	6.19		0.65	0.78	1.57	
	Ppg	WT	0.93	2.70	5.21		2.07	3.86	6.06		0.25	0.73	4.69	0.26
		HT	2.08	4.02	8.37	0.06	1.87	5.28	8.46	0.31	2.38	3.86	5.98	
		SNP	0.97	2.46	5.28		1.46	2.90	5.28		0.59	1.80	2.99	
	D	WT	1.13	3.02	5.78		1.11	2.83	3.86		4.06	6.92	8.77	0.29
		HT	0.87	1.62	4.14	0.84	0.79	1.54	7.29	0.35	0.87	2.46	3.56	
		SNP	0.96	2.54	8.30		1.87	3.21	8.88		0.53	1.27	7.73	
rs1800893 Block 3	U	Δct												0.76
		WT	14.28	14.28	17.35		14.28	14.28	17.45		14.28	14.28	16.15	
		HT	14.28	15.98	17.70	0.42	14.72	16.17	17.98	0.31	14.28	14.28	17.10	
	PHA	SNP	14.28	16.25	17.80		14.28	16.85	17.95		14.28	14.72	16.48	0.16
		WT	10.55	13.28	15.88		10.88	12.83	16.20		10.50	15.05	15.60	
		HT	10.00	13.30	14.90	0.77	10.80	13.75	15.25	0.92	8.65	11.55	13.10	
	LpA	SNP	10.90	12.95	14.93		10.80	12.70	15.60		11.00	13.30	14.55	0.41
		WT	13.45	15.68	17.00		13.45	15.40	16.90		15.10	16.85	17.40	
		HT	14.20	15.40	16.70	0.71	14.20	15.40	16.75	0.97	13.95	15.55	16.42	
	Ppg	SNP	14.78	16.00	16.98		11.65	15.75	16.30		14.90	16.75	17.15	0.11
		WT	13.65	15.23	16.30		13.10	14.70	15.75		15.25	16.30	16.60	
		HT	13.75	14.70	15.65	0.36	13.95	14.85	15.90	0.64	12.30	13.50	15.35	
D	SNP	14.65	15.50	16.00		13.08	15.78	16.10		15.00	15.30	15.50	0.87	
	WT	11.88	14.05	16.40		12.00	14.00	16.60		10.90	13.55	16.20		
	HT	12.60	15.80	16.50	0.62	12.60	15.60	16.50	0.80	12.45	15.80	16.20		
		SNP	12.40	15.05	16.20		7.70	15.50	16.20		12.40	14.90	16.20	
rs3024496 Block 3	Δct													
	WT	14.28	14.28	16.65		14.28	14.28	17.17		14.28	14.28	14.28		
U	HT	14.28	16.30	18.05	0.04	15.30	16.70	18.10	0.10	14.28	14.28	17.70	0.47	

PHA	SNP	14.28	16.00	16.85	0.91	14.28	16.25	17.95	0.85	14.28	15.15	16.35	0.79
	WT	10.15	12.68	15.60		10.60	12.80	16.25		9.20	12.23	15.10	
	HT	10.80	13.75	15.00		11.50	13.80	15.25		9.45	12.80	14.80	
LpA	SNP	10.80	12.95	15.25	0.83	7.90	12.75	15.60	0.68	11.28	13.20	14.53	0.46
	WT	12.50	15.25	17.00		13.45	15.33	16.85		12.85	15.70	17.40	
	HT	14.20	15.63	16.75		14.80	15.78	16.95		13.38	14.68	16.42	
Ppg	SNP	14.65	15.75	16.80	0.57	11.45	15.60	16.25	0.55	14.90	16.43	17.15	0.63
	WT	13.10	14.90	16.00		12.55	14.68	15.60		14.45	15.25	16.50	
	HT	13.75	15.00	15.90		13.95	15.00	15.90		11.70	14.08	16.03	
D	SNP	14.50	15.40	15.90	0.67	13.08	15.78	15.95	0.65	14.50	15.18	15.50	0.52
	WT	12.00	13.80	16.10		12.25	13.90	16.35		11.18	12.63	15.00	
	HT	12.30	15.80	16.50		13.30	15.90	16.60		12.30	12.45	15.80	
	SNP	12.50	15.05	16.20		10.15	14.05	15.85		13.60	15.05	16.20	
rs3024498 Block 4 U	Δ ct				0.44				0.73				0.49
	WT	14.28	14.28	17.45		14.28	16.50	17.90		14.28	14.28	16.15	
	HT	14.28	16.15	17.95		14.28	16.17	18.10		14.28	14.28	16.35	
	SNP	14.28	16.40	17.95	0.60	15.34	17.17	17.95	0.71	14.28	15.15	17.80	0.65
	WT	10.40	12.80	15.05		10.60	12.83	15.15		9.45	12.18	15.05	
	HT	10.20	13.65	15.30		12.80	14.00	15.55		9.50	11.65	14.50	
	SNP	12.70	13.30	15.10	0.40	11.75	13.90	15.75	0.35	13.10	13.30	13.60	0.90
	WT	13.50	15.28	16.83		13.90	15.30	16.75		13.55	15.60	17.40	
	HT	14.80	15.80	17.60		14.80	15.80	17.60		12.98	15.58	16.95	
	SNP	15.50	16.00	17.15	0.06	15.75	16.00	18.40	0.07	15.08	16.13	16.95	0.43
	WT	12.70	14.85	15.65		13.10	14.70	15.55		12.30	15.20	16.50	
	HT	14.30	15.80	16.85		14.30	15.80	16.70		14.23	16.10	16.85	
	SNP	14.75	15.28	15.90	0.55	13.68	15.90	16.98	0.57	14.75	15.03	15.28	0.66
	WT	12.00	14.00	16.20		12.00	15.50	16.60		12.00	12.45	16.20	
	HT	12.60	15.20	16.20		13.80	15.20	16.00		10.00	14.10	18.20	
	SNP	14.90	15.35	16.20		15.50	16.35	17.20		14.85	15.05	15.70	
Lymphocyte-activation gene 3 (LAG3)													
rs79309436	Δ ct				0.06				0.23				0.28
	WT	15.93	15.93	19.00		15.93	17.50	19.30		15.93	15.93	18.05	
	HT	15.93	18.80	19.45		17.50	19.00	19.55		15.93	16.79	19.25	
	SNP	15.93	18.55	18.95	0.95	15.93	18.75	18.95	0.71	15.93	18.35	21.80	0.33
	WT	8.70	11.10	13.05		8.70	11.10	13.55		8.40	11.35	13.05	
	HT	9.20	11.15	13.75		9.80	11.50	13.75		7.43	9.03	13.13	
	SNP	9.95	11.28	12.10	0.08	7.70	9.95	12.05	0.20	10.50	12.10	16.55	0.33
	WT	14.50	16.60	18.45		14.70	16.90	18.53		14.20	16.30	17.90	
	HT	16.30	17.80	19.30		16.75	18.10	19.30		14.55	16.30	16.55	
	SNP	17.18	18.35	20.05	0.06	17.15	18.33	19.50	0.12	17.20	18.90	20.60	0.63
	WT	14.60	16.67	17.60		14.75	16.80	17.80		14.18	16.42	17.58	
	HT	16.13	18.05	18.60		16.45	18.15	18.60		14.78	16.45	18.90	
	SNP	16.20	16.75	17.75		10.70	17.75	19.20		16.20	16.48	16.75	

D	WT	13.45	15.25	18.00	0.55	14.10	15.65	19.20	0.93	13.03	14.43	17.33	0.51	
	HT	13.70	17.00	18.50		13.70	17.10	18.50		13.63	15.75	18.30		
	SNP	16.30	16.90	17.90		16.90	16.90	16.90		16.30	17.10	17.90		
rs10494879		Δct												
U	WT	15.93	15.93	19.15	0.34	15.93	16.80	19.30	0.52	15.93	15.93	19.00	0.37	
	HT	15.93	18.05	19.20		17.05	18.75	19.50		15.93	15.93	18.05		
	SNP	15.93	18.55	19.55		15.93	18.75	19.40		15.93	18.35	19.70		
PHA	WT	8.70	11.10	12.95	0.97	9.05	11.00	13.68	0.37	8.28	10.95	12.48	0.27	
	HT	9.45	10.88	13.33		9.58	11.48	13.38		7.85	9.55	12.53		
	SNP	8.45	10.80	12.68		6.05	9.95	12.05		10.50	12.10	16.55		
LpA	WT	14.20	16.55	18.00	0.25	14.30	16.68	19.05	0.56	14.20	16.40	17.80	0.39	
	HT	16.20	17.30	18.90		16.30	17.50	18.90		14.73	16.30	17.80		
	SNP	14.90	18.35	20.45		14.90	18.33	19.90		15.88	18.83	20.53		
Ppg	WT	14.30	16.75	17.55	0.35	15.50	16.90	17.80	0.35	14.05	16.42	17.55	0.66	
	HT	14.80	16.65	18.30		16.13	16.60	18.25		14.75	16.90	19.20		
	SNP	16.20	17.75	18.60		17.75	18.60	19.20		15.65	16.48	17.68		
D	WT	13.58	15.38	18.50	0.91	14.55	15.65	19.40	0.74	13.00	14.25	17.75	0.63	
	HT	13.78	16.90	17.90		12.95	17.00	17.90		14.60	16.10	16.90		
	SNP	15.40	16.30	16.90		13.70	15.30	16.90		15.40	16.30	17.90		
rs1800890		Δct												
Block1 U	WT	15.93	15.93	19.05	0.14	15.93	16.93	19.20	0.35	15.93	15.93	19.00	0.36	
	HT	15.93	18.35	19.45		17.20	18.80	19.55		15.93	16.79	19.00		
	SNP	15.93	18.55	19.55		15.93	18.75	19.40		15.93	18.35	19.70		
PHA	WT	9.03	11.25	13.03	0.93	9.40	11.38	13.55	0.36	8.40	11.35	12.95	0.28	
	HT	9.45	11.28	14.13		9.50	11.45	14.50		8.85	9.45	11.40		
	SNP	8.68	10.80	12.68		6.05	9.95	12.05		10.50	12.10	16.55		
LpA	WT	14.90	16.55	18.00	0.14	14.90	16.80	19.15	0.56	14.20	16.13	17.80	0.13	
	HT	16.20	17.50	19.05		16.50	17.78	18.98		14.05	16.30	19.05		
	SNP	17.15	19.50	20.45		14.90	18.33	19.90		17.20	20.45	20.60		
Ppg	WT	15.50	16.80	17.80	0.47	15.55	17.05	17.98	0.83	14.05	16.42	17.55	0.47	
	HT	15.10	16.90	18.30		16.10	16.80	18.30		14.75	17.25	19.20		
	SNP	16.20	17.75	18.60		11.85	18.18	19.20		16.20	16.75	18.60		
D	WT	14.00	15.38	18.50	0.88	14.90	15.65	19.40	0.62	13.00	14.25	17.75	0.54	
	HT	13.70	16.90	17.90		13.33	17.05	18.20		15.40	16.10	16.90		
	SNP	14.88	16.60	17.40		13.45	15.18	16.90		16.30	17.10	17.90		
rs1800871		Δct												
Block 2 U	WT	15.93	17.65	19.20	0.28	15.93	18.55	19.20	0.11	15.93	15.93	19.08	0.27	
	HT	15.93	17.88	19.50		15.93	18.68	20.50		15.93	15.93	19.00		
	SNP	15.93	15.93	17.00		15.93	16.36	17.20		15.93	15.93	15.93		
PHA	WT	9.20	11.15	12.95	0.43	9.45	11.15	12.35	0.33	8.80	10.85	13.13	0.24	
	HT	10.15	11.48	13.75		10.23	11.78	14.60		8.85	11.35	12.00		
	SNP	7.55	9.70	14.50		8.50	10.28	14.50		5.10	5.10	5.10		
	WT	15.73	17.18	19.05		15.90	17.23	18.98		15.63	16.75	19.23		

LpA	HT	15.28	17.23	18.33	0.16	16.00	17.75	19.43	0.29	13.93	16.18	17.20	0.29
	SNP	12.30	15.45	16.55		13.15	15.45	16.55		11.35	13.88	16.40	
	WT	15.50	16.75	18.10		16.10	16.80	18.10		15.10	16.70	17.80	
Ppg	HT	16.15	17.40	18.15	0.32	16.45	17.80	18.20	0.59	14.30	17.20	17.85	0.09
	SNP	12.70	14.05	18.65		14.05	15.60	18.65		12.30	12.50	12.70	
	WT	14.10	16.35	17.90		13.58	17.00	18.70		14.60	16.20	17.90	
D	HT	14.25	16.95	20.10	0.04	16.90	19.30	20.50	0.05	13.00	13.65	17.75	0.05
	SNP	11.45	13.38	14.90		13.38	14.73	15.35		10.50	10.98	11.45	
rs1878672 Block 3 U	Δ ct												
	WT	15.93	15.93	19.15		15.93	16.80	19.30		15.93	15.93	15.93	
	HT	15.93	18.25	19.45	0.19	15.93	18.30	19.50	0.66	15.93	16.21	19.03	0.19
PHA	SNP	15.93	18.55	19.43		15.93	19.03	19.48		15.93	16.79	19.23	
	WT	9.70	11.38	13.05		9.55	11.50	15.05		10.30	11.35	12.00	
	HT	9.45	10.60	13.55	0.84	9.50	10.63	13.55	0.69	8.40	9.45	13.65	0.76
LpA	SNP	8.70	11.28	13.23		6.88	11.33	12.80		9.43	11.28	14.15	
	WT	14.10	16.55	18.45		13.65	17.20	19.68		14.20	16.40	17.80	
	HT	15.90	17.33	18.68	0.62	16.30	17.35	18.30	0.92	13.55	16.55	19.05	0.71
Ppg	SNP	14.90	17.15	19.50		14.90	17.83	19.50		15.90	16.30	19.40	
	WT	14.30	17.20	17.85		15.50	17.40	18.15		13.90	17.20	17.55	
	HT	15.95	16.63	18.25	0.62	16.10	16.55	18.30	0.59	15.80	16.70	17.60	0.68
D	SNP	15.10	17.75	18.70		16.65	18.10	18.70		15.10	16.48	18.60	
	WT	13.05	15.20	18.50		14.10	15.80	19.40		12.65	13.05	17.75	
	HT	15.25	16.95	18.90	0.30	14.95	17.00	18.90	0.88	16.40	16.90	18.00	0.11
	SNP	13.90	15.75	17.00		13.70	16.90	17.10		14.10	15.40	16.30	
rs1800893 Block 3 U	Δ ct												
	WT	15.93	15.93	19.15		15.93	15.93	19.30		15.93	15.93	15.93	
	HT	15.93	18.05	19.10	0.24	15.93	18.33	19.33	0.52	15.93	15.93	19.00	0.34
PHA	SNP	15.93	18.35	19.40		15.93	18.95	19.40		15.93	16.79	19.23	
	WT	9.55	11.25	12.93		9.05	11.38	15.05		10.30	11.35	12.00	
	HT	8.85	10.60	13.00	0.69	9.50	10.65	13.00	0.75	7.95	9.15	13.30	0.53
LpA	SNP	9.20	11.15	13.20		7.70	11.10	12.05		9.43	11.28	14.15	
	WT	14.10	16.40	18.00		13.20	16.40	18.55		15.00	16.50	17.85	
	HT	15.90	17.20	18.68	0.37	16.30	17.30	18.30	0.43	13.55	16.55	19.05	0.86
Ppg	SNP	15.40	17.18	19.70		14.90	18.90	19.90		15.90	16.30	19.40	
	WT	13.98	17.00	17.68		13.98	17.00	17.98		13.90	17.20	17.55	
	HT	15.95	16.67	18.10	0.47	16.15	16.73	18.20	0.56	14.80	16.42	17.60	0.69
D	SNP	15.10	17.75	18.60		11.85	18.10	19.20		15.10	16.48	18.60	
	WT	13.03	14.73	18.38		13.68	15.20	19.35		12.65	13.05	17.75	
	HT	15.25	17.00	18.90	0.10	14.95	17.45	18.90	0.72	16.40	16.90	18.00	0.09
	SNP	14.10	15.75	16.90		13.45	16.90	17.10		14.10	15.40	16.30	
rs3024496 Block 3 U	Δ ct												
	WT	15.93	15.93	18.55		15.93	15.93	19.25		15.93	15.93	15.93	
	HT	15.93	18.30	19.45	0.06	15.93	18.35	19.50	0.34	15.93	15.93	19.05	0.14

PHA	SNP	15.93	17.65	19.20		15.93	17.98	19.20		15.93	17.65	19.00	
	WT	9.40	11.25	13.65		8.70	11.15	16.30		10.30	11.48	13.05	
	HT	9.15	10.55	12.98	0.78	9.50	10.63	13.00	0.72	8.15	8.63	12.95	0.49
LpA	SNP	8.20	11.15	13.25		6.05	10.75	13.25		9.45	11.15	13.20	
	WT	13.88	16.40	18.23		13.20	16.40	19.55		14.20	16.40	17.80	
	HT	15.85	17.10	18.20	0.45	16.30	17.33	18.30	0.72	13.55	15.85	17.65	0.43
Ppg	SNP	14.90	17.15	19.40		13.20	17.15	19.50		15.90	16.75	19.40	
	WT	13.90	17.00	17.83		13.90	17.00	18.15		13.90	17.20	17.55	
	HT	15.65	16.50	18.10	0.51	16.10	16.55	18.20	0.70	14.75	16.15	16.90	0.50
D	SNP	15.10	17.68	18.60		11.85	18.10	18.65		15.10	16.75	18.60	
	WT	13.03	14.73	17.83		14.10	15.20	19.30		12.65	13.05	17.75	
	HT	14.95	16.95	18.90	0.19	14.95	17.00	18.90	0.68	15.70	16.40	18.00	0.26
rs3024498 Block 3 U	SNP	13.90	15.75	16.90		13.58	15.30	17.00		14.35	15.75	16.60	
	Δ ct												
	WT	15.93	15.93	19.05		15.93	18.25	19.50		15.93	15.93	18.53	
PHA	HT	15.93	17.65	19.40	0.26	15.93	18.55	19.45	0.78	15.93	16.50	19.05	0.27
	SNP	15.93	18.75	19.45		17.34	18.85	19.25		15.93	18.35	19.45	
	WT	9.40	11.10	12.95		9.40	10.75	12.50		8.40	11.38	13.05	
LpA	HT	8.85	11.50	14.50	0.86	9.80	11.55	13.75	0.75	7.35	9.25	15.10	0.76
	SNP	9.95	11.15	12.10		8.83	11.00	12.90		10.50	11.15	12.10	
	WT	14.35	16.65	18.00		14.50	16.90	18.45		14.20	16.35	17.90	
Ppg	HT	15.40	18.00	19.30	0.20	15.60	18.20	19.30	0.20	14.73	15.98	18.50	0.85
	SNP	16.30	17.20	19.50		17.15	18.50	19.50		15.43	16.75	18.90	
	WT	14.60	16.50	17.55		14.75	16.55	17.55		14.18	16.42	17.58	
D	HT	16.30	18.38	18.63	<0.01	16.45	18.30	18.60	0.02	14.75	18.60	19.20	0.42
	SNP	15.65	17.25	18.25		14.23	18.23	18.95		15.65	16.48	17.28	
	WT	13.45	15.25	17.90		13.78	15.65	19.25		13.03	14.43	17.33	
D	HT	13.70	17.05	18.50	0.45	14.33	17.05	18.20	0.79	11.85	16.18	20.50	0.63
	SNP	16.10	16.60	17.90		16.90	17.95	19.00		15.75	16.20	17.10	

1.Q, first quartile; Med, median; 3.Q, third quartile; p(KW), p-value from Kruskal-Wallis test. CBMCs all, CBMCs of all mothers, not stratified for maternal atopy. Bold p-values, data are presented in overview table II and table E2, respectively. Δ ct, delta CT; fd, fold difference.

Table E2: Cytokine secretion [pg/ml] of Interleukin-5 (IL-5), Interferon-gamma (IFN- γ), Tumor-necrosis factor-alpha (TNF- α) and Granulocyte-macrophage colony-stimulating factor (GM-CSF) stratified for maternal atopy (raw data).

Interleukin-5 (IL-5)													
LD-Block/SNP	Genotype	CBMCs all				CBMCs of non-atopic mothers				CBMCs of atopic mothers			
Stimulation		1.Q	Med	3.Q	p(KW)	1.Q	Med	3.Q	p(KW)	1.Q	Med	3.Q	p(KW)
rs79309463													
U	WT	0.01	0.13	0.18	<0.01	0.01	0.11	0.16	0.02	0.01	0.14	0.22	0.23
	HT	0.01	0.01	0.13		0.01	0.01	0.13		0.01	0.02	0.19	
	SNP	0.01	0.02	0.13		0.01	0.02	0.19		0.01	0.07	0.13	
PHA	WT	9.44	29.28	57.24	0.46	5.93	31.54	64.70	0.52	12.34	28.42	54.36	0.83
	HT	7.89	26.58	40.76		7.51	26.41	51.98		11.53	27.90	40.76	
	SNP	4.85	25.52	27.19		4.18	25.52	27.19		12.55	23.31	31.36	
LpA	WT	3.20	7.44	15.33	0.03	2.92	8.25	22.17	0.05	3.35	6.02	13.16	0.52
	HT	1.54	6.25	12.97		1.55	7.93	13.25		1.12	4.23	9.09	
	SNP	2.40	2.57	4.99		1.00	2.54	2.57		3.63	4.92	5.12	
Ppg	WT	14.81	31.37	67.92	0.56	16.92	41.27	74.61	0.42	13.84	23.70	50.27	0.99
	HT	8.04	25.35	60.78		6.32	29.92	63.81		11.26	22.95	43.39	
	SNP	12.94	30.18	38.27		5.52	30.18	41.72		17.28	29.47	37.79	
D	WT	6.19	10.97	26.26	0.07	5.07	10.93	30.92	0.05	6.72	11.63	16.10	0.70
	HT	2.60	6.60	22.10		2.27	5.91	18.08		2.93	9.06	35.16	
	SNP	4.50	5.24	9.70		1.84	5.24	9.70		4.71	6.47	13.42	
D+LpA	WT	6.31	10.19	24.13	0.12	4.37	10.19	30.33	0.53	7.67	10.00	17.73	0.09
	HT	2.92	7.49	17.67		3.57	10.53	18.08		1.07	7.49	15.59	
	SNP	2.83	6.76	10.28		3.67	9.51	10.28		2.83	4.80	6.76	
rs10494879													
U	WT	0.01	0.11	0.18	0.38	0.01	0.13	0.16	0.05	0.01	0.11	0.18	0.59
	HT	0.01	0.01	0.16		0.01	0.01	0.13		0.01	0.14	0.22	
	SNP	0.01	0.09	0.16		0.01	0.07	0.16		0.05	0.13	0.20	
PHA	WT	6.86	27.10	64.68	0.75	6.86	31.01	77.76	0.99	9.76	20.93	54.36	0.43
	HT	10.08	28.39	56.10		5.49	28.26	63.08		16.63	30.69	40.33	
	SNP	7.13	25.52	49.14		7.13	26.36	52.37		4.85	20.25	36.35	
LpA	WT	3.49	7.90	15.30	0.09	3.58	8.42	21.12	0.34	3.38	6.38	10.85	0.28
	HT	2.90	7.93	17.20		2.95	8.59	15.36		2.90	5.82	18.38	
	SNP	1.31	3.62	8.28		1.31	2.57	26.58		1.60	4.24	5.12	
Ppg	WT	16.71	32.59	64.59	0.56	12.67	38.89	70.62	0.96	16.71	23.88	50.27	0.38
	HT	14.68	31.86	67.65		13.10	35.74	70.37		14.68	25.35	60.72	
	SNP	5.28	27.69	53.67		5.28	41.72	69.46		9.08	19.00	32.50	
	WT	6.59	11.52	22.43		6.36	10.88	32.53		6.72	12.49	16.10	

D	HT	4.71	10.16	23.12	0.03	3.96	9.97	22.59	0.21	6.51	10.84	44.76	0.04	
	SNP	2.19	4.84	11.00		1.84	5.01	11.95		2.88	4.71	7.00		
	D+LpA	WT	7.14	10.71	24.13	0.52	6.23	10.43	30.33	0.80	8.08	13.82	17.73	0.18
		HT	3.16	9.87	20.28		3.16	11.00	20.28		4.34	8.54	40.88	
	SNP	3.67	7.86	14.54		5.73	9.51	14.54		2.83	4.80	6.76		
rs1800890														
Block1	WT	0.01	0.12	0.18	0.08	0.01	0.12	0.17	0.06	0.01	0.12	0.18	0.70	
	U	HT	0.01	0.01		0.14	0.01	0.01		0.13	0.01	0.05		0.22
	SNP	0.01	0.12	0.19		0.01	0.06	0.16		0.07	0.13	0.24		
PHA	WT	9.44	27.93	60.65	1.00	7.17	35.02	64.70	0.77	10.08	23.30	38.86	0.66	
	HT	6.06	28.39	40.76		5.49	28.17	49.14		16.80	32.96	39.90		
	SNP	9.33	26.30	44.83		7.13	26.23	37.28		11.53	26.37	56.11		
LpA	WT	3.39	7.90	15.36	0.11	3.66	8.69	22.17	0.11	2.90	6.31	10.85	0.81	
	HT	2.61	6.46	13.52		2.45	8.24	13.52		2.61	5.82	13.83		
	SNP	1.56	4.12	8.28		1.31	2.61	8.28		3.01	4.92	9.20		
Ppg	WT	16.71	35.62	67.92	0.49	18.55	41.97	75.10	0.33	13.84	23.70	50.27	0.91	
	HT	11.26	25.72	60.72		11.02	33.44	67.65		11.26	21.83	43.86		
	SNP	5.52	24.66	42.58		5.28	24.97	53.67		14.66	24.66	37.79		
D	WT	6.59	11.52	26.26	0.03	6.48	10.93	29.30	0.04	6.72	12.21	16.10	0.44	
	HT	3.95	9.68	22.16		3.95	9.55	22.40		4.81	9.78	21.76		
	SNP	2.77	4.84	10.35		2.02	4.01	10.35		3.81	5.44	13.42		
D+LpA	WT	6.61	10.43	23.66	0.20	5.94	10.43	30.33	0.31	7.88	11.74	17.34	0.25	
	HT	3.16	8.54	16.63		3.18	11.75	18.49		2.92	7.49	9.50		
	SNP	2.95	6.76	10.28		3.31	6.80	9.90		2.83	6.76	66.17		
rs1800871														
Block 2	WT	0.01	0.10	0.16	0.87	0.01	0.07	0.13	0.36	0.01	0.13	0.22	0.66	
	U	HT	0.01	0.02		0.19	0.01	0.02		0.19	0.01	0.02		0.22
	SNP	0.02	0.10	0.16		0.06	0.10	0.16		0.01	0.09	0.17		
PHA	WT	10.08	28.63	56.11	0.20	7.00	28.49	61.87	0.18	12.34	32.96	47.61	0.68	
	HT	4.50	23.30	37.87		2.67	12.56	35.33		7.91	23.70	46.12		
	SNP	12.13	32.69	71.07		16.09	45.96	87.16		7.72	20.66	47.60		
LpA	WT	2.54	6.14	15.35	0.29	2.54	8.28	21.36	0.18	2.40	4.85	9.31	0.20	
	HT	3.44	6.42	11.89		2.77	5.53	11.59		4.49	8.50	13.21		
	SNP	5.09	12.13	23.42		7.90	16.28	23.42		4.85	5.09	15.88		
Ppg	WT	12.21	32.65	66.13	0.99	12.60	40.12	74.45	0.74	11.78	21.16	48.29	0.33	
	HT	13.04	25.33	63.28		10.78	25.76	64.35		20.05	25.33	58.02		
	SNP	16.12	32.60	55.98		21.63	44.23	67.66		7.29	17.43	30.67		
D	WT	4.50	9.55	19.03	0.43	3.24	9.70	22.59	0.45	5.96	9.39	16.32	0.68	
	HT	6.33	10.35	22.78		6.29	9.29	22.43		6.60	12.55	26.94		
	SNP	5.37	12.86	29.31		4.99	18.02	29.69		6.14	9.88	19.56		
D+LpA	WT	3.67	9.50	18.49	0.64	3.18	10.28	26.35	0.50	5.75	8.34	13.82	0.57	
	HT	6.31	9.66	17.73		5.56	7.65	15.79		8.28	15.59	17.73		
	SNP	4.52	14.78	28.58		7.36	17.42	31.36		4.52	14.78	28.58		

rs1878672 Block 3	U	WT	0.01	0.13	0.18		0.01	0.13	0.16		0.01	0.11	0.19	
		HT	0.01	0.01	0.16	0.22	0.01	0.01	0.13	0.03	0.01	0.15	0.22	0.85
		SNP	0.01	0.10	0.18		0.01	0.09	0.16		0.01	0.13	0.23	
	PHA	WT	9.44	27.70	60.65		7.17	31.01	74.65		12.34	25.90	54.36	
		HT	5.78	27.92	59.59	0.93	5.49	29.27	64.70	0.64	6.06	17.76	38.86	0.73
		SNP	7.13	27.68	40.76		5.02	26.36	42.45		16.45	30.69	40.76	
	LpA	WT	3.49	6.38	15.30		3.21	7.04	18.37		4.25	6.38	11.11	
		HT	3.13	7.92	15.52	0.05	3.20	8.24	17.20	0.21	3.05	6.31	13.83	0.29
		SNP	1.53	3.89	9.10		1.49	2.64	9.45		1.61	4.15	6.25	
	Ppg	WT	11.82	25.11	64.59		9.12	29.71	71.35		16.71	23.88	50.27	
		HT	16.19	38.46	67.65	0.20	16.92	41.90	70.37	0.54	14.68	28.11	60.72	0.38
		SNP	5.40	21.92	48.13		5.28	24.27	54.66		7.99	20.70	37.31	
rs1800893 Block 3	U	WT	0.01	0.13	0.18		0.01	0.13	0.16		0.01	0.06	0.19	
		HT	0.01	0.02	0.16	0.35	0.01	0.01	0.13	0.06	0.01	0.15	0.22	0.73
		SNP	0.01	0.10	0.19		0.01	0.08	0.16		0.01	0.13	0.22	
	PHA	WT	9.44	27.40	64.68		7.17	27.10	74.65		12.34	27.70	57.24	
		HT	8.26	30.41	63.40	0.77	8.62	33.50	64.70	0.36	6.06	17.76	38.86	0.70
		SNP	9.33	27.68	38.35		4.18	25.52	36.47		16.45	28.47	40.76	
	LpA	WT	3.66	7.86	15.30		3.58	8.94	20.07		4.25	6.42	10.85	
		HT	3.28	8.37	19.22	<0.01	3.39	8.49	20.06	0.06	3.05	6.31	18.38	0.22
		SNP	1.49	3.51	8.28		1.31	2.61	8.75		1.55	3.89	5.75	
	Ppg	WT	12.67	25.21	64.59		10.49	36.60	69.27		16.71	23.70	46.68	
		HT	16.40	43.00	82.19	0.03	16.92	44.59	84.30	0.19	16.40	34.88	71.39	0.16
		SNP	5.28	21.16	41.72		5.28	23.25	53.67		6.60	18.54	32.50	
rs3024496 Block 3	U	WT	5.37	10.97	26.94		4.99	10.45	29.69		6.72	12.55	16.10	
		HT	5.80	11.40	27.58	<0.01	5.14	11.22	27.92	0.02	6.60	11.58	27.58	0.18
		SNP	2.64	5.91	11.95		1.65	4.01	10.35		3.12	6.41	13.80	
	D	WT	6.23	10.43	21.83		3.14	8.16	24.13		8.28	14.78	19.52	
		HT	6.03	13.11	27.43	0.05	6.31	15.32	31.67	0.10	5.75	8.08	15.59	0.10
		SNP	2.94	7.17	9.90		2.95	6.80	10.28		2.92	7.17	9.50	
	D+LpA	WT	0.01	0.13	0.18		0.01	0.13	0.18		0.01	0.13	0.19	
		HT	0.01	0.01	0.16	0.13	0.01	0.01	0.13	0.03	0.01	0.15	0.22	0.97
		SNP	0.01	0.10	0.19		0.01	0.07	0.16		0.01	0.13	0.23	
		WT	9.75	26.23	60.65		7.17	27.10	77.76		11.21	23.70	46.23	

PHA	HT	4.69	28.63	64.70	0.92	5.49	30.41	64.70	0.46	4.69	16.80	39.90	0.66
	SNP	8.62	27.19	38.18		4.18	25.34	36.47		16.45	32.96	40.76	
LpA	WT	3.49	7.82	15.30		3.49	8.22	15.37		4.25	6.38	11.11	
	HT	3.20	8.24	18.15	0.02	3.30	8.37	19.11	0.08	3.05	6.31	13.83	0.34
Ppg	SNP	1.31	3.62	8.75		1.16	2.57	9.45		2.01	4.50	5.94	
	WT	9.16	25.11	65.77		9.08	29.71	70.62		16.71	23.88	50.27	
D	HT	18.28	41.20	67.65	0.06	18.71	44.46	73.08	0.25	16.40	28.11	60.72	0.34
	SNP	5.52	20.70	41.72		5.28	22.22	54.66		9.18	19.83	32.50	
D+LpA	WT	6.59	10.88	22.43		5.68	9.73	28.33		6.90	12.55	16.10	
	HT	5.38	11.52	25.35	0.02	5.14	11.31	27.92	0.03	6.57	12.06	22.10	0.32
D+LpA	SNP	2.77	5.94	12.21		1.84	3.94	9.70		4.50	8.03	13.80	
	WT	7.14	10.71	19.52		5.56	8.46	24.13		8.97	15.30	18.63	
D+LpA	HT	5.16	11.00	23.19	0.09	5.74	15.56	24.77	0.26	2.93	7.79	9.19	0.05
	SNP	2.95	6.76	10.28		2.95	5.73	14.54		2.92	7.17	9.50	
rs3024498													
Block 4	WT	0.01	0.13	0.18		0.01	0.10	0.16		0.01	0.14	0.23	
	HT	0.01	0.01	0.16	0.12	0.01	0.01	0.13	0.18	0.01	0.08	0.22	0.29
U	SNP	0.01	0.05	0.13		0.01	0.05	0.16		0.01	0.05	0.13	
	WT	9.44	28.42	56.11		6.86	29.82	74.65		12.34	27.70	47.61	
PHA	HT	7.89	30.54	63.72	0.16	7.13	29.27	63.72	0.36	11.53	32.96	90.99	0.39
	SNP	4.85	21.60	26.37		5.02	17.86	26.36		4.85	21.87	26.37	
LpA	WT	3.20	6.74	14.94		2.74	8.02	21.12		3.39	6.17	12.14	
	HT	2.90	7.61	13.66	<0.01	3.20	8.49	17.20	0.06	2.76	5.24	11.38	0.15
Ppg	SNP	1.00	2.47	4.99		1.25	2.21	5.43		0.79	3.63	4.99	
	WT	13.84	27.69	64.59		12.67	38.89	73.08		14.26	23.70	49.28	
D	HT	11.26	29.92	71.39	0.15	11.02	38.04	82.19	0.30	11.26	25.35	71.39	0.54
	SNP	4.72	17.28	38.27		4.53	17.85	47.70		11.78	17.28	37.31	
D+LpA	WT	5.91	10.93	21.92		4.99	10.88	29.31		6.72	11.63	16.10	
	HT	3.94	10.35	22.21	0.03	3.51	8.74	20.15	0.13	5.96	12.66	41.30	0.11
D+LpA	SNP	1.46	4.71	9.70		1.65	4.34	10.83		0.55	4.71	8.03	
	WT	7.02	10.19	21.83		4.37	10.19	30.33		7.88	10.00	17.34	
D+LpA	HT	3.50	8.50	18.08	0.14	4.00	10.53	18.49	0.66	2.92	8.50	15.59	0.04
	SNP	2.83	5.22	10.28		3.03	9.51	14.54		1.07	2.83	6.76	
Interferon-gamma (IFN-γ)													
rs79309463	WT	0.01	0.01	1.02		0.01	0.01	1.51		0.01	0.01	0.01	
	HT	0.01	0.01	1.03	0.29	0.01	0.01	0.77	0.29	0.01	1.02	1.99	<0.01
U	SNP	0.01	1.02	1.51		0.01	0.01	1.03		0.55	1.27	4.83	
	WT	13.34	61.27	160.34		15.05	67.41	175.05		9.07	59.37	156.14	
PHA	HT	14.90	93.95	209.93	0.38	21.60	87.59	214.26	0.60	14.63	124.02	209.93	0.55
	SNP	20.50	55.55	58.75		20.50	56.45	58.75		15.01	38.25	95.57	
LpA	WT	5.22	35.48	95.98		9.24	48.22	111.50		3.00	17.29	52.31	
	HT	5.52	38.14	92.10	0.65	5.74	46.12	94.45	0.38	5.31	16.86	74.43	0.75
LpA	SNP	7.69	49.41	127.67		49.41	98.95	146.96		4.42	24.68	85.76	

	Ppg	WT	14.07	43.50	116.80	0.89	16.26	47.64	130.71	0.74	8.59	30.56	61.60	0.98
		HT	10.93	47.78	127.84		10.93	55.86	137.75		11.43	27.92	118.38	
		SNP	12.05	56.58	136.02		56.58	96.62	136.86		9.28	26.09	88.08	
	D	WT	6.99	43.28	120.75	0.86	12.18	54.64	133.32	0.50	6.28	19.57	67.71	0.42
		HT	11.38	49.37	105.38		9.36	49.73	100.77		13.84	39.05	112.00	
		SNP	9.74	67.28	104.06		67.28	100.11	104.06		6.81	25.98	90.94	
	D+LpA	WT	31.35	75.51	145.74	0.73	51.20	120.84	152.49	0.76	10.40	46.98	98.41	0.30
		HT	54.34	105.68	139.64		54.34	93.28	139.64		43.60	107.17	152.10	
		SNP	47.37	101.10	138.89		67.28	101.10	113.34		47.37	93.13	138.89	
rs10494879														
	U	WT	0.01	0.01	0.89	0.04	0.01	0.01	1.45	0.97	0.01	0.01	0.01	<0.01
		HT	0.01	0.01	1.51		0.01	0.01	1.51		0.01	0.01	1.82	
		SNP	0.01	1.01	1.99		0.01	0.01	1.03		1.27	1.99	3.24	
	PHA	WT	8.59	57.52	154.50	0.41	7.45	58.43	154.50	0.73	9.01	51.49	111.40	0.30
		HT	14.90	104.18	209.93		14.90	101.34	198.28		16.62	104.18	452.46	
		SNP	16.20	56.45	135.59		20.50	73.80	229.63		9.27	20.94	124.02	
	LpA	WT	5.56	24.62	95.79	0.91	7.45	48.68	117.50	1.00	2.84	15.19	53.12	0.79
		HT	5.63	40.99	94.53		7.10	46.67	105.78		3.48	26.51	69.33	
		SNP	3.48	21.16	106.34		7.69	49.41	106.34		3.40	5.19	84.74	
Ppg	WT	15.70	42.51	108.75	0.97	15.70	49.09	128.59	0.93	13.77	28.17	59.21	0.75	
	HT	11.83	44.77	118.38		16.27	49.91	127.84		11.43	27.92	102.15		
	SNP	6.18	40.13	136.86		5.74	96.62	174.23		6.35	9.96	86.45		
D	WT	6.99	39.33	118.44	0.58	7.03	50.39	136.30	0.70	6.28	19.57	86.06	0.57	
	HT	12.15	49.37	120.33		12.15	54.85	130.33		10.05	35.84	88.81		
	SNP	7.03	23.62	104.06		9.36	47.87	104.06		6.77	9.66	86.63		
D+LpA	WT	26.44	63.45	145.74	0.57	51.20	127.12	152.49	0.66	9.06	28.19	63.45	0.10	
	HT	47.37	106.43	152.10		54.34	108.78	143.78		45.49	106.43	167.93		
	SNP	47.37	101.10	138.89		67.28	101.10	113.34		47.37	93.13	138.89		
rs1800890 Block 1														
	U	WT	0.01	0.01	0.79	0.09	0.01	0.01	1.45	0.95	0.01	0.01	0.01	<0.01
		HT	0.01	0.01	1.82		0.01	0.01	1.51		0.01	0.01	1.99	
		SNP	0.01	0.73	1.99		0.01	0.01	1.03		0.55	1.75	2.25	
	PHA	WT	8.59	57.52	154.50	0.33	17.69	62.92	154.50	0.77	8.59	48.63	111.40	0.21
		HT	8.59	57.52	154.50		17.69	62.92	154.50		8.59	48.63	111.40	
		SNP	18.61	104.42	203.97		14.90	93.95	198.28		37.39	118.78	209.93	
	LpA	WT	14.75	46.17	122.52	0.92	16.20	56.45	109.45	0.99	9.27	20.94	135.59	0.79
		HT	5.74	33.50	81.69		7.45	47.61	114.24		3.48	17.29	53.12	
		SNP	5.74	44.54	96.96		7.10	51.49	98.31		3.70	37.15	74.43	
Ppg	WT	16.26	43.50	116.80	0.85	15.98	49.74	126.41	0.92	16.31	33.69	61.60	0.79	
	HT	11.83	47.78	120.71		19.96	56.17	132.82		5.20	27.64	102.15		
	SNP	6.18	29.76	136.02		5.74	76.60	136.86		6.35	9.96	88.08		
		WT	7.03	39.33	115.50		8.85	46.84	130.19		6.99	20.85	67.71	

D	HT	12.15	52.33	123.26	0.58	12.15	56.98	132.62	0.87	10.05	35.84	112.00	0.66	
	SNP	6.77	36.66	106.03		6.12	69.89	106.03		6.77	9.66	90.94		
	WT	27.32	68.39	137.31		49.42	120.84	144.76		9.73	34.71	68.39		
	HT	51.69	104.30	160.06		54.34	101.43	160.06		47.37	107.17	152.10		
D+LpA	SNP	67.28	102.75	168.15	0.23	70.49	101.93	140.75	0.97	47.37	138.89	1447.74	0.06	
rs1800871 Block 2	WT	0.01	0.01	1.02	0.19	0.01	0.01	1.03	0.51	0.01	0.01	1.02	0.27	
	HT	0.01	0.01	1.99		0.01	0.45	1.59		0.01	0.01	2.25		
	U	SNP	0.01	0.01		0.23	0.01	0.01		0.74	0.01	0.01		0.01
	WT	18.61	78.60	182.90		20.50	81.49	198.28		14.63	77.36	160.34		
PHA	HT	7.23	54.29	131.16	0.32	6.70	51.71	131.16	0.46	8.80	58.75	140.28	0.40	
	SNP	22.81	62.44	124.06		29.56	101.13	135.48		8.41	25.94	74.97		
LpA	WT	4.88	42.85	96.96	0.77	7.69	51.49	105.78	0.84	3.48	16.86	60.83	0.85	
	HT	5.92	23.66	80.39		7.10	36.16	114.87		4.40	16.24	70.31		
Ppg	SNP	5.65	22.77	44.78	0.38	13.80	29.25	70.05	0.78	3.57	13.64	32.81	0.45	
	WT	9.57	36.34	117.73		10.93	49.74	134.00		6.51	26.26	64.16		
	HT	16.26	54.50	120.71		23.80	58.02	127.84		12.60	42.02	119.55		
	SNP	12.51	26.49	73.63		12.51	35.72	130.41		11.64	24.37	35.32		
D	WT	7.10	45.37	120.33	0.98	9.36	52.71	118.44	0.83	7.03	23.62	127.49	0.66	
	HT	7.03	41.17	115.50		11.03	44.66	146.51		4.64	25.94	86.06		
D+LpA	SNP	10.52	31.16	98.12	0.51	28.76	43.28	142.93	0.43	8.40	17.60	36.19	0.18	
	WT	47.37	85.13	138.89		51.69	85.13	135.44		43.60	77.26	151.32		
	HT	12.33	107.17	152.10		74.94	134.89	165.86		5.63	48.63	107.17		
	SNP	26.44	46.43	107.34		62.06	92.52	129.15		9.06	26.44	41.23		
rs1878672 Block 3	WT	0.01	0.01	0.88	0.15	0.01	0.01	1.02	0.81	0.01	0.01	0.01	0.05	
	HT	0.01	0.01	1.82		0.01	0.01	1.51		0.01	0.01	1.99		
	U	SNP	0.01	0.27		1.27	0.01	0.45		1.01	0.01	0.08		1.99
	WT	9.01	54.34	137.37		16.28	58.43	149.53		9.01	43.59	97.49		
PHA	HT	14.90	86.34	179.02	0.48	21.60	90.15	190.59	0.85	8.59	84.35	153.49	0.37	
	SNP	16.20	58.75	137.46		16.20	58.75	161.02		14.63	67.70	135.59		
LpA	WT	5.56	20.89	58.29	0.20	8.35	40.23	87.12	0.81	2.53	7.44	41.43	0.10	
	HT	6.18	50.45	101.60		7.10	51.49	111.50		3.70	49.41	101.60		
Ppg	SNP	4.17	28.66	101.51	0.22	7.69	49.41	105.78	0.71	3.32	10.02	44.86	0.19	
	WT	14.07	35.96	68.96		15.98	43.56	113.38		8.59	27.03	51.08		
	HT	18.14	57.15	133.55		19.96	57.15	137.75		16.31	54.61	120.71		
	SNP	6.35	29.76	126.66		7.26	96.62	136.86		6.18	15.43	64.16		
D	WT	6.99	31.52	73.32	0.18	10.67	43.28	130.04	0.73	4.08	10.52	45.56	0.07	
	HT	13.21	54.85	130.13		12.15	64.44	130.33		13.57	52.53	118.62		
D+LpA	SNP	7.03	44.86	107.99	0.02	9.36	67.28	107.99	0.77	6.51	19.54	128.40	<0.01	
	WT	18.99	48.63	130.14		48.44	77.69	145.74		7.35	22.72	43.91		
	HT	59.61	125.55	164.40		56.83	115.72	164.40		103.64	144.53	159.61		
	SNP	47.37	99.76	129.30		67.28	102.75	117.58		43.60	47.37	138.89		

rs1800893 Block 3	U	WT	0.01	0.01	1.01		0.01	0.01	1.45		0.01	0.01	0.01	
		HT	0.01	0.01	1.82	0.29	0.01	0.01	1.51	0.88	0.01	0.01	1.99	0.10
		SNP	0.01	0.08	1.51		0.01	0.45	1.03		0.01	0.07	1.82	
	PHA	WT	9.07	55.93	137.37		13.13	58.43	138.75		9.07	48.63	111.40	
		HT	18.61	93.95	203.97	0.41	28.54	101.34	214.26	0.50	8.59	84.35	160.34	0.49
		SNP	15.05	58.75	137.46		15.63	57.60	134.31		14.63	79.84	254.97	
	LpA	WT	5.74	21.30	58.29		7.45	25.48	87.12		2.84	9.91	38.14	
		HT	6.18	51.90	101.60	0.17	7.10	52.31	111.50	0.70	3.70	49.41	101.60	0.15
		SNP	3.48	27.67	104.06		4.96	57.54	106.34		3.40	14.60	45.05	
	Ppg	WT	13.77	27.88	68.96		13.23	31.77	113.38		13.77	27.60	51.08	
		HT	24.20	58.58	133.55	0.05	25.26	74.42	137.75	0.24	16.31	42.31	120.71	0.32
		SNP	6.18	18.54	120.55		5.74	76.60	136.86		6.35	16.36	62.88	
rs3024496 Block 3	U	WT	0.01	0.01	1.01		0.01	0.01	1.45		0.01	0.01	0.01	
		HT	0.01	0.01	1.82	0.30	0.01	0.01	1.51	0.92	0.01	0.01	1.99	0.10
		SNP	0.01	0.07	1.51		0.01	0.01	1.01		0.01	0.08	1.91	
	PHA	WT	7.45	54.34	138.75		7.45	67.41	154.50		6.85	33.95	80.33	
		HT	18.91	97.03	201.13	0.37	28.30	93.95	198.28	0.85	18.61	100.11	209.93	0.14
		SNP	15.63	69.30	133.38		16.20	58.75	131.16		14.63	79.84	135.59	
	LpA	WT	4.88	20.89	68.87		7.45	31.05	114.24		2.84	7.44	41.43	
		HT	6.18	52.31	101.60	0.21	7.10	51.90	100.72	0.91	3.70	52.31	102.85	0.14
		SNP	3.48	21.16	98.95		4.96	49.41	106.34		3.40	14.60	47.14	
	Ppg	WT	13.77	34.42	78.30		14.07	38.79	123.26		13.77	28.17	51.08	
		HT	16.31	56.17	132.82	0.29	23.80	58.12	132.82	0.67	11.43	31.81	120.71	0.62
		SNP	6.18	19.38	132.77		5.74	96.62	144.16		6.35	16.36	57.18	
rs3024498 Block 3	U	WT	6.99	28.17	86.06		8.85	42.04	138.89		6.28	11.07	45.56	
		HT	12.15	57.80	130.13	0.21	12.15	57.80	123.26	0.71	13.21	48.58	130.13	0.12
		SNP	6.77	36.66	112.20		9.36	67.28	104.06		6.51	23.62	128.40	
	D	WT	18.99	48.44	135.44		48.44	130.14	150.96		7.35	22.72	43.91	
		HT	59.23	120.84	162.23	0.07	56.83	109.51	160.06	0.93	107.17	144.53	167.12	<0.01
		SNP	47.37	98.41	129.30		67.28	107.34	129.30		43.60	51.74	138.89	
	D+LpA	WT	0.01	0.01	1.02		0.01	0.01	1.51		0.01	0.01	0.04	
		HT	0.01	0.01	1.27	0.33	0.01	0.01	0.91	0.87	0.01	0.52	1.99	0.01
		SNP	0.01	0.33	1.51		0.01	0.01	0.81		0.08	1.27	3.97	
		WT	9.07	58.43	160.34		13.13	62.92	179.02		9.07	54.34	111.40	

PHA	HT	14.90	91.40	198.28	0.67	28.30	88.84	198.28	0.78	10.93	100.11	209.93	0.59
	SNP	20.94	56.00	124.02		31.10	54.38	84.10		20.94	89.79	135.59	
LpA	WT	5.22	25.95	90.43		10.49	46.63	107.78		2.92	13.79	48.72	
	HT	5.31	38.14	94.45	0.43	5.52	50.39	105.78	0.59	5.09	27.50	77.41	0.31
	SNP	19.00	48.82	125.63		33.61	52.82	122.96		5.52	44.35	125.63	
	WT	13.77	35.96	108.75		15.70	45.49	128.59		7.39	27.60	59.12	
Ppg	HT	11.63	55.86	140.55	0.55	19.96	58.12	144.16	0.80	7.86	17.69	120.71	0.69
	SNP	12.05	60.37	132.77		26.94	60.84	116.74		12.05	52.15	132.77	
	WT	6.94	43.08	116.97		13.77	51.69	130.04		5.88	18.41	52.59	
	HT	11.38	41.17	120.33	0.73	7.95	52.33	130.33	0.71	12.22	26.22	118.62	0.28
D	SNP	9.74	57.70	104.06		33.67	62.54	102.09		7.10	48.23	128.40	
	WT	34.71	70.57	148.35		51.20	120.84	164.54		9.73	43.91	80.93	
D+LpA	HT	54.34	111.74	152.10	0.37	53.02	104.39	141.71	0.50	107.17	144.92	342.71	0.11
	SNP	47.37	63.07	113.34		53.53	67.28	113.34		43.60	47.37	138.89	
Tumor necrosis factor-alpha (TNF-~)													
rs79309463	WT	0.11	0.71	1.37		0.11	0.65	1.27		0.01	0.91	1.38	
	HT	0.01	0.10	1.03	0.01	0.01	0.02	1.03	0.01	0.01	0.29	0.97	0.62
U	SNP	0.01	0.91	1.12		0.63	0.97	1.12		0.01	0.46	1.19	
	WT	44.37	367.52	1125.23		35.43	300.43	1021.46		67.57	586.22	1767.69	
PHA	HT	88.52	426.70	1267.89	0.34	75.75	376.59	1587.14	0.43	188.29	854.94	1185.80	0.51
	SNP	37.96	229.08	422.07		37.96	229.08	381.47		54.69	251.64	538.08	
	WT	373.44	1013.83	1777.27		423.36	943.73	1706.09		265.12	1131.02	1970.03	
	HT	358.07	888.83	1857.59	0.06	357.01	856.27	1670.83	0.03	412.89	974.66	1904.77	0.74
LpA	SNP	198.88	365.10	530.60		122.84	326.87	365.10		316.39	698.99	1157.65	
	WT	1392.98	2195.90	3427.11		1458.74	2328.86	3379.51		1364.08	1975.01	3479.13	
Ppg	HT	1133.66	2137.56	3036.45	0.01	1133.66	2089.98	2808.92	<0.01	1203.10	2607.95	3036.45	0.64
	SNP	929.49	1131.97	1789.40		546.41	929.49	1131.97		1416.75	1797.28	2151.77	
	WT	495.75	1095.66	2223.45		538.55	888.14	2146.29		415.03	1308.83	2378.35	
	HT	426.03	864.22	1687.70	0.04	422.71	772.67	1295.21	0.06	456.93	1241.73	1813.45	0.43
D	SNP	257.53	395.68	983.59		257.53	286.05	452.73		309.70	689.64	1261.07	
	WT	424.48	1027.81	1503.13		435.10	811.24	1272.74		397.18	1216.02	1797.98	
D+LpA	HT	470.22	977.95	1520.70	0.10	450.77	1060.70	1859.66	0.33	481.19	702.12	1520.70	0.22
	SNP	193.81	290.50	1075.90		262.46	290.50	1075.90		193.81	316.45	439.08	
rs10494879													
	WT	0.11	0.65	1.16		0.11	0.77	1.23		0.01	0.58	1.15	
	HT	0.01	0.39	1.15	0.25	0.01	0.42	1.15	0.22	0.01	0.32	1.38	0.45
U	SNP	0.02	0.79	1.47		0.02	0.63	1.17		0.28	1.19	1.79	
	WT	38.32	449.69	1125.23		35.43	444.74	1125.23		64.70	529.85	1058.79	
PHA	HT	102.73	368.93	1282.22	0.67	75.75	181.47	1150.35	0.98	199.71	912.97	1319.73	0.19
	SNP	37.96	300.43	545.91		62.63	338.51	545.91		28.18	81.20	654.08	
	WT	412.18	1062.37	1935.65		445.08	1003.05	2058.65		371.22	1131.02	1721.07	
	HT	376.28	981.27	1902.98	0.03	553.57	938.35	1621.50	0.07	369.02	1134.57	2150.66	0.33
LpA	SNP	225.77	423.36	1029.22		326.87	418.24	913.88		151.37	698.99	1232.92	

	Ppg	WT	1364.08	2295.46	3336.83	0.04	1450.58	2403.49	3427.11	0.10	1302.73	2187.43	3162.36	0.33
		HT	1392.98	2270.20	3253.58		1491.92	2254.23	3135.92		1392.98	2810.56	3298.49	
		SNP	929.49	1330.50	2498.37		917.57	1212.97	2549.86		1187.30	1797.28	2261.57	
	D	WT	495.75	1132.10	2223.45	0.06	547.41	979.62	2414.67	0.04	415.03	1269.13	1783.81	0.66
		HT	470.61	907.13	1940.48		515.02	864.22	1783.09		402.80	1241.73	2719.30	
		SNP	346.33	493.21	1095.23		346.33	454.73	672.30		309.70	1151.46	1621.98	
	D+LpA	WT	397.52	1044.38	1797.98	0.05	421.62	1042.32	2353.05	0.15	391.40	1209.13	1391.49	0.30
		HT	501.08	1013.18	1528.77		565.90	1054.52	1447.57		439.19	840.04	1657.44	
		SNP	262.46	439.08	674.37		290.50	470.22	674.37		193.81	316.45	439.08	
rs1800890														
Block 1	U	WT	0.11	0.80	1.23	0.01	0.11	0.78	1.23	0.06	0.01	0.94	1.30	0.19
		HT	0.01	0.29	1.03		0.01	0.33	1.03		0.01	0.20	0.97	
		SNP	0.01	0.94	1.47		0.01	0.80	1.23		0.46	1.19	1.79	
	PHA	WT	43.07	368.93	1099.90	0.96	36.47	355.58	1021.46	0.99	64.70	544.97	1316.66	0.76
		HT	83.60	347.73	1150.35		37.17	231.90	1076.46		211.12	854.94	1185.80	
		SNP	50.30	340.95	1120.61		62.63	300.43	545.91		29.60	422.07	2407.30	
	LpA	WT	463.22	1042.71	1777.27	0.22	501.17	943.73	1757.48	0.12	371.22	1144.80	1935.65	0.85
		HT	279.86	886.18	1901.19		279.86	826.35	1621.50		369.02	1098.09	2066.27	
		SNP	225.77	428.63	1351.22		225.77	391.67	913.88		316.39	1039.34	1357.78	
	Ppg	WT	1405.63	2414.02	3479.13	0.10	1458.74	2303.93	3381.97	0.10	1364.08	2430.01	3970.00	0.45
		HT	1144.19	2137.56	3133.29		1138.93	2204.88	3194.75		1203.10	2028.41	3036.45	
		SNP	1131.97	1616.77	2498.37		929.49	1286.80	2093.45		1559.95	1914.96	2553.16	
	D	WT	631.18	1098.09	2223.45	0.11	640.02	888.14	2146.29	0.04	495.75	1329.86	2397.54	0.64
		HT	393.99	801.90	1846.51		435.67	847.58	1669.99		330.28	790.34	1999.51	
		SNP	316.19	570.81	1428.94		271.79	452.08	642.11		689.64	1428.94	1873.52	
	D+LpA	WT	451.99	1042.32	1447.31	0.13	451.99	968.84	1360.54	0.15	425.37	1216.02	1594.74	0.75
		HT	427.90	945.96	1485.06		424.48	1048.40	1449.41		481.19	702.12	1520.70	
		SNP	193.81	439.08	1075.90		222.42	415.31	875.14		193.81	439.08	3008.32	
rs1800871														
Block 2	U	WT	0.01	0.54	1.23	0.93	0.01	0.55	1.17	0.82	0.01	0.39	1.38	0.84
		HT	0.01	0.65	1.27		0.01	0.65	1.27		0.01	0.44	1.41	
		SNP	0.11	0.61	1.06		0.06	0.38	1.13		0.54	0.97	1.06	
	PHA	WT	67.45	381.47	1282.22	0.79	50.30	334.93	1196.57	0.86	81.20	586.22	1282.22	0.92
		HT	43.72	264.27	986.78		41.92	183.33	830.96		99.40	407.53	1078.40	
		SNP	25.34	476.30	1240.40		25.34	394.90	1156.77		276.22	801.88	1240.40	
	LpA	WT	357.01	845.72	1616.50	0.58	365.10	886.18	1643.56	0.86	198.88	723.85	1364.33	0.28
		HT	412.89	1122.13	1797.05		279.86	877.29	1706.09		529.46	1326.61	1951.67	
		SNP	279.49	1148.39	1605.10		279.49	827.07	1421.08		793.94	1580.54	1828.36	
	Ppg	WT	1311.16	1994.44	3072.43	0.54	1251.74	2081.30	3026.40	0.67	1330.50	1874.39	3162.36	0.82
		HT	1302.73	2669.88	3427.11		1133.66	2669.88	3588.33		1354.18	2572.40	3215.89	
		SNP	1260.77	1785.66	2948.83		1294.53	1785.66	2757.01		1102.63	2171.23	3114.69	
	D	WT	415.03	888.14	1538.55	0.28	451.42	752.27	1290.67	0.36	404.96	1095.66	1846.51	0.76
		HT	497.30	1177.64	2223.45		497.30	996.92	2234.30		400.63	1475.88	1977.79	

D+LpA	SNP	359.15	1157.04	2110.22	0.89	331.07	840.19	2110.22	0.77	771.59	1382.37	2571.38	0.88	
	WT	397.18	923.66	1425.47		290.50	913.97	1425.47		397.18	950.81	1536.83		
	HT	458.25	725.06	1520.70		458.25	899.03	2212.88		459.33	702.12	1264.82		
	SNP	359.64	1044.38	1797.98		389.74	737.85	1768.80		359.64	1382.04	1797.98		
rs1878672 Block 3		WT	0.06	0.94	1.20	0.39	0.11	0.90	1.23	0.09	0.01	0.97	1.17	0.53
U	HT	0.01	0.42	1.15	0.01		0.41	1.03	0.01		0.65	1.47		
	SNP	0.01	0.57	1.23	0.33		0.63	1.23	0.01		0.39	1.47		
PHA	WT	44.37	449.69	1352.00	0.95		36.47	449.69	1778.39		0.59	64.70	410.87	
	HT	67.45	282.32	1150.35		43.07	178.15	1002.57	211.12	735.33		1316.66		
	SNP	62.63	358.33	1122.97		50.30	264.76	486.60	81.20	538.08		1253.56		
LpA	WT	448.47	1062.37	1935.65	0.06	504.29	1035.72	2155.33	0.15	371.22	1131.02	1609.41	0.12	
	HT	375.65	1037.55	1904.77		358.07	826.35	1616.50		412.89	1555.43	2150.66		
	SNP	212.33	497.74	1241.67		326.87	530.60	1186.44		185.76	464.87	1351.22		
	WT	1405.63	2424.54	3479.13	0.02	1458.74	2612.73	3559.97	0.09	1302.73	2187.43	3136.73	0.11	
Ppg	HT	1308.88	2286.17	3298.49		1251.74	2155.52	2980.87		1313.43	2987.24	3468.91		
	SNP	1060.60	1492.80	2486.83		1006.35	1326.94	2475.28		1203.10	1594.64	2498.37		
D	WT	404.82	1213.09	2234.30	0.02	547.41	1132.50	2465.26	0.03	386.13	1269.13	1783.81	0.06	
	HT	575.98	976.49	1940.48		497.30	809.70	1669.99		778.77	1729.37	3255.97		
	SNP	298.89	513.23	1128.04		286.05	456.72	1095.23		298.89	748.41	1538.55		
D+LpA	WT	397.52	1040.25	1797.98	0.04	397.52	913.97	2493.22	0.23	409.49	1216.02	1386.77	0.14	
	HT	513.20	1054.52	1511.92		476.15	1054.52	1386.63		514.36	1111.41	6400.06		
	SNP	262.46	475.71	1064.18		262.46	540.11	1064.18		286.48	439.08	977.95		
rs1800893 Block 3		WT	0.01	0.65	1.17	0.71	0.11	0.79	1.23	0.17	0.01	0.35	1.15	0.53
U	HT	0.01	0.44	1.17	0.01		0.41	1.12	0.01		0.65	1.47		
	SNP	0.01	0.65	1.38	0.35		0.81	1.23	0.01		0.55	1.38		
PHA	WT	44.37	453.82	1185.80	0.95		36.47	449.69	1587.14		0.59	64.70	514.72	
	HT	67.45	323.39	1021.46		43.07	248.17	659.34	211.12	735.33		1316.66		
	SNP	50.30	364.60	1305.40		37.96	229.08	545.91	81.20	654.08		1357.24		
LpA	WT	448.47	1094.76	1797.05	0.07	515.77	1094.76	2238.19	0.07	371.22	1077.03	1609.41	0.25	
	HT	412.18	981.27	1706.09		375.65	786.35	1592.05		412.89	1359.13	2150.66		
	SNP	198.88	449.39	1351.22		225.77	420.80	1029.22		192.32	522.57	1357.78		
	WT	1450.58	2414.02	3336.83	0.02	1487.11	2612.73	3381.97	0.04	1302.73	2005.48	3136.73	0.10	
Ppg	HT	1313.43	2453.65	3422.19		1251.74	2204.37	3253.58		1593.61	3084.87	3468.91		
	SNP	1044.10	1457.00	2498.37		929.49	1229.81	2475.28		1266.80	1692.02	2553.16		
D	WT	395.03	1269.13	2234.30	0.04	547.41	1245.92	2465.26	0.01	386.13	1269.13	1607.69	0.10	
	HT	619.22	976.49	1846.51		515.02	780.99	1295.21		778.77	1674.38	3255.97		
	SNP	286.05	513.23	1319.33		271.79	452.08	816.36		298.89	983.59	1705.40		
D+LpA	WT	378.58	1126.76	2005.43	0.06	397.52	1040.25	2493.22	0.15	359.64	1222.90	1391.49	0.25	
	HT	522.14	1062.41	1511.92		520.97	1060.64	1425.47		523.30	1520.70	1778.04		
	SNP	246.37	460.14	1082.55		230.28	415.31	1075.90		286.48	460.14	1089.20		
rs3024496														

Block 3	U	WT	0.06	0.94	1.23	0.28	0.11	0.81	1.23	0.13	0.01	0.97	1.23	0.66
		HT	0.01	0.41	1.12		0.01	0.42	1.03		0.01	0.33	1.47	
		SNP	0.01	0.55	1.23		0.33	0.65	1.23		0.01	0.37	1.19	
	PHA	WT	44.37	449.69	1352.00	0.97	36.47	449.69	1587.14	0.59	58.92	410.87	899.11	0.63
		HT	75.75	275.80	1021.46		67.45	181.47	1002.57		211.12	559.89	1316.66	
		SNP	37.96	376.59	1122.97		35.74	170.48	545.91		81.20	654.08	1253.56	
	LpA	WT	448.47	1127.14	1935.65	0.04	477.97	1003.05	2159.50	0.08	448.47	1166.59	1609.41	0.53
		HT	412.18	987.87	1621.50		412.18	938.35	1592.05		369.02	1144.80	2096.94	
		SNP	185.76	464.87	1351.22		130.06	418.24	1029.22		192.32	522.57	1357.78	
	Ppg	WT	1405.63	2403.49	3479.13	0.03	1450.58	2248.47	3427.11	0.08	1405.63	2424.54	3479.13	0.26
		HT	1364.08	2270.20	3162.36		1514.73	2229.30	3058.40		1313.43	2829.14	3298.49	
		SNP	1006.35	1444.14	2549.86		917.57	1212.97	2549.86		1266.80	1692.02	2553.16	
D	WT	404.82	1269.13	2397.54	0.02	476.12	1056.06	2439.97	0.02	395.03	1308.83	1977.79	0.30	
	HT	631.18	938.75	1846.51		619.22	880.86	1669.99		777.12	1357.52	3060.25		
	SNP	292.47	454.73	1305.23		286.05	451.42	611.92		298.89	983.59	1705.40		
D+LpA	WT	397.52	1044.38	1797.98	0.05	397.52	707.45	2493.22	0.10	409.49	1216.02	1386.77	0.41	
	HT	523.30	1054.52	1445.72		667.94	1062.41	1386.63		505.42	612.71	11022.07		
	SNP	262.46	439.08	1075.90		230.28	431.32	1075.90		286.48	460.14	1089.20		
rs3024498														
Block 3	U	WT	0.01	0.65	1.23	0.44	0.11	0.65	1.23	0.28	0.01	0.62	1.30	0.66
		HT	0.01	0.35	1.17		0.01	0.35	1.15		0.01	0.60	1.93	
		SNP	0.01	0.61	0.97		0.46	0.80	1.05		0.01	0.28	0.91	
	PHA	WT	38.32	449.69	1352.00	0.79	33.56	367.52	1352.00	0.90	67.57	559.89	1316.66	0.46
		HT	93.43	214.02	970.99		75.75	178.15	639.21		188.29	854.94	1253.56	
		SNP	37.96	305.28	654.08		118.13	305.28	1102.84		28.18	251.64	654.08	
	LpA	WT	370.12	1042.71	1946.73	0.04	393.92	965.80	2058.65	0.11	317.07	1122.82	1828.36	0.23
		HT	412.89	886.18	1670.83		357.01	786.35	1224.46		438.88	1329.41	1999.79	
		SNP	198.88	399.50	1009.07		224.86	447.85	1019.15		198.88	352.16	964.07	
	Ppg	WT	1392.98	2093.45	3336.83	<0.01	1466.90	2254.23	3336.83	0.01	1338.76	1874.39	3315.64	0.52
		HT	1144.19	2453.65	3298.49		1138.93	2220.85	3763.72		1203.10	2810.56	3133.29	
		SNP	929.49	1172.47	1805.16		737.95	1069.16	1364.36		1044.10	1797.28	2143.55	
D	WT	439.79	1103.84	2228.88	0.02	529.69	979.62	2234.30	0.12	404.96	1269.13	2152.51	0.06	
	HT	456.72	778.77	1780.38		451.42	678.40	1290.67		777.12	1590.64	2041.63		
	SNP	257.53	424.21	983.59		271.79	693.06	1027.82		223.71	332.72	983.59		
D+LpA	WT	397.35	1042.32	1476.27	0.07	411.00	873.85	1476.27	0.52	394.29	1149.17	1584.77	0.08	
	HT	502.25	937.69	1483.21		470.22	972.91	1445.72		523.30	840.04	1520.70		
	SNP	193.81	364.79	1015.36		262.46	913.97	1075.90		118.67	193.81	439.08		
Granulocyte macrophage colony-stimulating factor (GM-CSF)														
rs79309463	U	WT	0.01	0.01	1.46	0.72	0.01	0.01	3.01	0.42	0.01	0.01	0.01	0.79
		HT	0.01	0.01	1.06		0.01	0.01	0.69		0.01	0.01	5.25	
		SNP	0.01	0.01	0.01		0.01	0.01	0.01		0.01	0.01	3.67	
	PHA	WT	0.01	5.43	49.37	0.02	0.01	1.49	40.57	0.03	0.01	9.60	60.88	0.23
		HT	0.01	5.44	62.04		0.01	6.25	104.13		0.01	4.13	32.03	

LpA	SNP	0.01	0.01	0.01	0.07	0.01	0.01	0.01	0.06	0.01	0.01	7.70	0.68
	WT	0.01	4.03	20.34		0.01	4.13	20.12		0.01	3.93	27.09	
	HT	0.01	2.28	12.14		0.01	1.49	12.90		0.01	3.13	9.27	
	SNP	0.01	0.01	0.01		0.01	0.01	0.01		0.01	1.17	5.36	
Ppg	WT	5.42	77.92	344.52	0.28	5.28	70.58	494.30	0.45	7.10	91.85	335.67	0.44
	HT	1.76	85.56	332.10		0.26	9.45	473.34		16.41	123.53	247.18	
	SNP	0.01	40.78	98.13		0.01	64.99	98.13		3.36	23.75	79.74	
D	WT	0.11	16.45	103.93	0.03	0.01	14.87	73.33	0.02	2.28	28.15	139.54	0.56
	HT	0.01	9.90	103.48		0.01	8.50	87.91		0.04	26.81	175.61	
	SNP	0.01	0.01	0.01		0.01	0.01	0.01		0.01	9.54	62.46	
D+LpA	WT	0.01	3.51	73.91	0.06	0.01	1.96	50.59	0.12	0.01	8.59	104.63	0.10
	HT	0.01	0.27	67.15		0.01	4.82	103.77		0.01	0.01	3.26	
	SNP	0.01	0.01	0.01		0.01	0.01	0.01		0.01	0.01	0.01	
rs10494879													
U	WT	0.01	0.01	0.78	0.78	0.01	0.01	1.46	0.93	0.01	0.01	0.01	0.28
	HT	0.01	0.01	3.21		0.01	0.01	2.78		0.01	0.01	5.12	
	SNP	0.01	0.01	6.10		0.01	0.01	0.16		0.01	3.06	7.77	
PHA	WT	0.01	4.46	44.34	0.09	0.01	4.97	100.93	0.28	0.01	3.08	34.35	0.08
	HT	0.01	7.24	126.50		0.01	6.08	49.37		2.80	19.76	155.11	
	SNP	0.01	0.01	11.36		0.01	0.14	2.84		0.01	0.01	15.38	
LpA	WT	0.01	5.25	22.93	0.23	0.01	6.34	23.29	0.09	0.01	0.01	13.35	0.72
	HT	0.01	3.02	14.14		0.01	2.34	12.90		0.01	5.76	20.65	
	SNP	0.01	0.01	8.39		0.01	0.01	0.69		0.01	3.46	8.83	
Ppg	WT	8.07	77.92	335.67	0.34	6.81	58.73	235.47	0.74	11.46	177.47	344.52	0.28
	HT	4.13	99.68	488.28		3.64	98.08	521.94		8.11	99.68	327.43	
	SNP	0.01	40.02	119.35		0.01	9.27	156.40		3.36	40.40	99.80	
D	WT	0.01	25.72	208.03	0.07	0.01	28.15	227.93	0.02	1.32	15.81	139.54	0.98
	HT	0.25	10.37	96.24		0.25	10.28	43.48		0.34	19.21	144.74	
	SNP	0.01	0.22	55.33		0.01	0.01	1.42		0.01	37.20	111.61	
D+LpA	WT	0.01	5.61	111.14	0.05	0.01	8.02	130.24	0.14	0.01	2.52	104.63	0.31
	HT	0.01	3.75	46.66		0.01	4.29	79.16		0.01	1.77	33.06	
	SNP	0.01	0.01	0.07		0.01	0.01	0.07		0.01	0.01	0.01	
rs1800890													
Block 1	WT	0.01	0.01	0.69	0.64	0.01	0.01	1.46	0.89	0.01	0.01	0.01	0.27
	HT	0.01	0.01	3.64		0.01	0.01	2.78		0.01	0.01	5.12	
	SNP	0.01	0.01	6.10		0.01	0.01	0.16		0.01	3.06	7.77	
PHA	WT	0.01	4.46	37.25	0.56	0.01	1.90	50.07	0.52	0.01	5.98	35.90	0.87
	HT	0.01	5.46	62.04		0.01	5.44	49.37		0.01	5.48	126.50	
	SNP	0.01	0.27	28.80		0.01	0.26	2.84		0.01	11.36	47.22	
LpA	WT	0.01	4.97	23.29	0.64	0.01	5.80	21.70	0.43	0.01	0.87	38.49	0.97
	HT	0.01	2.39	12.90		0.01	2.28	11.13		0.01	5.36	14.64	
	SNP	0.01	0.63	9.27		0.01	0.17	12.14		1.17	4.26	8.83	
	WT	7.10	81.07	344.52		5.24	61.39	367.89		13.20	163.64	344.52	

Ppg	HT	2.34	85.56	361.20	0.55	3.64	110.60	488.28	0.65	0.01	55.52	213.13	0.36
	SNP	0.26	52.89	156.40		0.01	37.13	156.40		23.37	60.85	182.94	
	WT	0.01	25.72	206.14		0.01	21.64	157.73		2.18	45.33	206.14	
	HT	0.11	9.80	95.95	0.26	0.11	8.14	49.59	0.15	0.34	10.03	105.96	0.78
	SNP	0.01	1.15	73.64		0.01	0.22	10.27		9.54	41.74	111.61	
	WT	0.01	4.01	121.68		0.01	4.01	121.68		0.01	8.22	151.12	
D+LpA	HT	0.01	1.77	40.73	0.18	0.01	4.23	67.15	0.33	0.01	0.27	27.13	0.52
	SNP	0.01	0.01	0.16		0.01	0.01	0.12		0.01	0.01	38.98	
rs1800871													
Block 2		WT	0.01	0.01	0.26		0.01	0.01	1.06		0.01	0.01	0.01
U	HT	0.01	0.01	5.61	0.04	0.01	0.01	3.64	0.35	0.01	0.01	7.88	0.06
	SNP	0.01	0.01	0.09		0.01	0.01	0.81		0.01	0.01	0.01	
	WT	0.01	5.44	67.08		0.01	5.12	73.63		0.01	13.53	66.73	
PHA	HT	0.01	4.18	15.21	0.44	0.01	3.07	15.21	0.57	0.01	4.27	22.47	0.58
	SNP	0.01	3.41	14.79		0.01	0.01	14.79		3.41	7.32	21.87	
LpA	WT	0.01	0.41	12.90		0.01	0.69	13.63		0.01	0.01	12.53	
	HT	0.01	5.98	13.35	0.45	0.01	5.53	20.12	0.51	0.01	6.64	12.16	0.51
	SNP	0.01	0.01	22.51		0.01	0.01	12.28		0.01	19.25	40.90	
Ppg	WT	2.97	72.94	329.77		3.64	84.43	488.28		2.05	56.27	274.89	
	HT	7.10	102.86	380.72	0.69	3.96	70.58	521.94	0.66	13.94	142.15	280.29	0.27
	SNP	2.09	57.10	244.17		2.09	23.17	105.18		74.91	278.96	632.11	
D	WT	0.01	10.17	97.65		0.01	10.08	83.86		0.01	10.26	103.93	
	HT	1.42	27.29	139.54	0.21	0.38	22.89	105.23	0.38	4.00	48.09	206.14	0.54
	SNP	0.01	5.61	85.88		0.01	5.61	72.10		0.01	42.95	247.92	
D+LpA	WT	0.01	0.92	67.15		0.01	4.25	111.14		0.01	0.01	38.98	
	HT	0.01	2.52	45.27	0.78	0.01	0.09	39.70	0.79	0.27	3.26	45.27	0.51
	SNP	0.01	0.01	104.63		0.01	0.04	74.70		0.01	0.01	104.63	
rs1878672													
Block 3		WT	0.01	0.01	0.78		0.01	0.01	1.02		0.01	0.01	0.69
U	HT	0.01	0.01	5.04	0.83	0.01	0.01	3.64	0.86	0.01	0.01	5.25	0.97
	SNP	0.01	0.01	0.52		0.01	0.01	0.16		0.01	0.01	6.10	
	WT	0.01	6.11	55.48		0.01	6.11	100.93		0.01	5.61	34.35	
PHA	HT	0.01	4.68	45.79	0.80	0.01	4.84	42.21	0.26	0.01	4.13	66.73	0.61
	SNP	0.01	3.03	32.03		0.01	0.27	6.23		0.01	14.73	47.22	
LpA	WT	0.01	4.68	22.93		0.01	6.16	23.29		0.01	0.87	12.18	
	HT	0.01	4.19	13.63	0.20	0.01	2.39	11.13	0.19	0.01	7.95	27.09	0.45
	SNP	0.01	0.01	8.83		0.01	0.01	5.42		0.01	0.26	9.27	
Ppg	WT	8.36	106.04	344.52		7.57	61.39	228.08		11.46	192.25	380.72	
	HT	4.41	75.98	411.13	0.23	3.64	96.57	500.31	0.81	10.06	72.94	213.13	0.09
	SNP	0.14	25.14	182.04		1.76	10.26	156.40		0.01	40.02	247.18	
D	WT	0.01	25.72	170.20		0.01	28.15	208.03		1.32	15.81	139.54	
	HT	0.68	14.87	99.57	0.04	0.11	12.93	49.59	0.03	2.28	85.25	206.14	0.38
	SNP	0.01	0.87	44.29		0.01	0.01	6.51		0.01	13.20	97.65	

D+LpA	WT	0.01	3.76	104.63	0.14	0.01	3.76	111.14	0.47	0.01	8.22	89.27	0.23		
	HT	0.01	3.75	79.16		0.01	4.77	79.16		0.01	1.77	187.06			
	SNP	0.01	0.01	4.25		0.01	0.01	4.25		0.01	0.01	3.26			
rs1800893 Block 3	U	WT	0.01	0.01	1.02	0.90	0.01	0.01	1.46	0.99	0.01	0.01	0.69	0.93	
	HT	0.01	0.01	5.04	0.01		0.01	3.64	0.01		0.01	5.25			
	SNP	0.01	0.01	0.87	0.01		0.01	0.87	0.01		0.01	0.01			
	PHA	WT	0.01	5.43	42.21	0.96	0.01	6.11	62.04	0.50	0.01	4.41	34.35	0.55	
		HT	0.01	5.42	58.05		0.01	5.40	49.37		0.01	5.98	66.73		
		SNP	0.01	4.35	63.70		0.01	0.27	7.05		0.01	15.38	174.34		
	LpA	WT	0.01	5.24	21.70	0.42	0.01	6.70	23.29	0.21	0.01	2.00	9.15	0.68	
		HT	0.01	3.02	13.35		0.01	2.28	10.81		0.01	7.95	27.09		
		SNP	0.01	0.29	12.14		0.01	0.17	12.14		0.01	1.29	10.90		
	Ppg	WT	8.07	94.67	338.54	0.24	6.94	61.39	228.08	0.67	11.46	185.26	380.72	0.13	
		HT	4.96	81.70	411.13		3.64	96.57	500.31		16.41	75.98	213.13		
		SNP	0.01	25.14	161.79		0.26	9.77	156.40		0.01	40.40	224.73		
	D	WT	0.01	23.29	208.03	0.20	0.01	25.72	227.93	0.11	2.18	15.81	103.93	0.67	
		HT	0.61	13.11	96.52		0.25	11.71	43.48		1.42	63.91	206.14		
		SNP	0.01	1.42	91.95		0.01	0.22	12.82		0.01	19.06	105.86		
	D+LpA	WT	0.01	3.14	107.89	0.42	0.01	0.01	111.14	0.73	0.01	13.92	104.63	0.45	
		HT	0.01	3.75	60.74		0.01	4.25	67.15		0.01	0.27	54.33		
		SNP	0.01	0.01	15.73		0.01	0.04	4.33		0.01	0.01	27.13		
	rs3024496 Block 3	U	WT	0.01	0.01	0.95	0.92	0.01	0.01	1.46	0.97	0.01	0.01	0.69	0.96
		HT	0.01	0.01	5.04	0.01		0.01	3.64	0.01		0.01	5.25		
SNP		0.01	0.01	0.87	0.01	0.01		0.87	0.01	0.01		3.06			
PHA		WT	0.01	7.32	55.48	0.64	0.01	7.51	84.01	0.22	0.01	7.32	35.13	0.38	
		HT	0.01	4.51	28.04		0.01	5.12	28.04		0.01	1.75	13.53		
		SNP	0.01	3.21	47.22		0.01	0.14	7.05		0.01	15.38	126.50		
LpA		WT	0.01	5.80	27.09	0.25	0.01	6.16	23.65	0.22	0.01	4.68	38.49	0.83	
		HT	0.01	2.39	11.13		0.01	2.34	10.81		0.01	7.59	13.35		
		SNP	0.01	0.01	12.14		0.01	0.01	12.14		0.01	1.29	10.90		
Ppg		WT	7.10	78.85	335.67	0.38	1.84	29.53	194.80	0.44	25.63	192.25	380.72	0.09	
		HT	5.14	85.56	473.34		5.14	129.70	521.94		10.06	52.47	198.67		
		SNP	0.01	10.26	247.18		0.26	9.27	161.79		0.01	40.40	287.31		
D		WT	0.01	28.15	206.14	0.08	0.01	25.72	217.98	0.05	2.18	48.09	180.18	0.53	
		HT	1.96	13.28	85.25		0.74	13.28	49.59		2.28	26.41	233.85		
		SNP	0.01	1.15	73.64		0.01	0.01	6.51		0.01	19.06	102.61		
D+LpA		WT	0.01	2.52	73.91	0.22	0.01	0.01	61.47	0.38	0.01	8.22	89.27	0.42	
		HT	0.01	4.78	91.17		0.01	5.46	79.16		0.01	0.14	319.78		
		SNP	0.01	0.01	4.33		0.01	0.01	4.33		0.01	0.01	27.13		
rs3024498 Block 3		WT	0.01	0.01	1.46		0.01	0.01	2.78		0.01	0.01	0.35		

U	HT	0.01	0.01	1.17	0.28	0.01	0.01	0.87	0.29	0.01	0.01	5.43	0.69
	SNP	0.01	0.01	0.01		0.01	0.01	0.01		0.01	0.01	0.01	
	WT	0.01	6.35	55.48		0.01	5.40	67.08		0.01	7.83	38.60	
PHA	HT	0.01	3.67	28.04	0.07	0.01	2.84	28.04	0.13	0.01	4.13	32.03	0.48
	SNP	0.01	0.01	1.78		0.01	0.01	0.90		0.01	0.01	15.38	
	WT	0.01	4.99	23.29		0.01	5.53	23.29		0.01	2.78	20.87	
LpA	HT	0.01	2.39	10.81	<0.01	0.01	0.69	10.81	<0.01	0.01	4.26	10.71	0.32
	SNP	0.01	0.01	0.01		0.01	0.01	0.01		0.01	0.01	2.32	
	WT	5.14	74.12	335.67		5.14	64.17	473.34		5.98	77.52	318.65	
Ppg	HT	2.99	92.62	346.65	0.38	1.76	10.26	521.94	0.59	16.41	198.67	327.43	0.44
	SNP	0.01	23.75	118.69		1.16	33.68	108.74		0.01	23.75	118.69	
	WT	0.27	16.36	106.33		0.01	16.91	105.23		2.18	15.81	139.54	
D	HT	0.38	28.15	109.30	<0.01	0.01	10.48	83.86	0.01	1.42	70.97	233.85	0.16
	SNP	0.01	0.01	0.07		0.01	0.01	0.01		0.01	0.04	19.06	
	WT	0.01	3.51	67.69		0.01	4.00	50.59		0.01	2.89	89.27	
D+LpA	HT	0.01	1.77	79.16	0.05	0.01	2.25	116.36	0.21	0.01	1.77	27.13	0.17
	SNP	0.01	0.01	0.01		0.01	0.01	0.07		0.01	0.01	0.01	

1.Q, first quartile; Med, median; 3.Q, third quartile; p(KW), p-value from Kruskal-Wallis test. CBMCs all, CBMCs of all mothers, not stratified for maternal atopy. Bold p-values, data are presented in overview table II and table E2, respectively.

Table E3. Influence of the investigated genetic variants of *IL-10* on Th2, Th1, GM-CSF and TNF- α cytokine secretion and gene expression of Treg-associated genes stratified for CBMC of atopic/non-atopic mothers

LD-Block/ SNP	CBMC of non-atopic /atopic mothers	IL-5		IFN- γ		TNF- $\sim$		GM-CSF		Treg- marker genes	
rs79309463	0	↓	U* LpA* # D* #		n.d.	↑ ↓	U* LpA* # Ppg* # D #	↓	PHA* LpA # D* #		n.d.
	1	↓	D+LpA #	↑	U* #		n.d.	↓	D+LpA	↓	FOXP3 PHA* #
rs10494879	0	↓	U*		n.d.	↓	LpA # Ppg # D* #	↓	LpA # D* #	↓	GITR U
	1	↓	D* #	↑	U* D+LpA		n.d.	↓	PHA	↓	FOXP3 GITR (fd) (fd) PHA # D # PHA D #
Block 1 rs1800890	0	↓	U D* #		n.d.	↓	Ppg # D* #		n.d.	↓	GITR U
	1		n.d.	↑	U* D+LpA #		n.d.		n.d.	↓	FOXP3 PHA* # Ppg* # D #
Block 2 rs1800871	0		n.d.		n.d.		n.d.		n.d.	↑	FOXP3 GITR LAG3 D* D D* Ppg* LpA
	1		n.d.		n.d.		n.d.		n.d.	↑	FOXP3 LAG3 D* # Ppg
Block 3 rs1878672	0	↓	U* D		n.d.	↓	U Ppg # D* #	↓	D* #	↑	FOXP3 (fd) D
	1	↓	D+LpA #	↑	U* D D+LpA*	↓	D	↓	Ppg #	↓	FOXP3 D
Block 3 rs1800893	0	↓	U LpA # D* D+LpA		n.d.	↓	LpA # Ppg* # D* #		n.d.	↑	FOXP3 (fd) PHA
	1	↓	D+LpA #	↑	D D+LpA*	↓	Ppg D		n.d.	↓	LAG3 D
Block 3 rs3024496	0	↓	U* LpA D*		n.d.	↓	LpA # Ppg # D* # D+LpA	↓	D* #	↓	GITR U
	1	↓	D+LpA* #	↑	U D+LpA*		n.d.	↓	Ppg #		n.d.
Block 4 rs3024498	0	↓	LpA		n.d.	↓	Ppg* #	↓	LpA* D*	↓	GITR LAG3 Ppg # Ppg*
	1	↓	D+LpA* #	↑	U* #	↓	D D+LpA #		n.d.		

0: CBMCs of non-atopic mothers; 1: CBMCs of atopic mothers.

↑: secretion/expression upregulated in homozygous carriers of the minor allele;

↓: secretion/expression downregulated in homozygous carriers of the minor allele;

U, unstimulated; PHA, phytohemagglutinin; LpA, Lipid A; Ppg, peptidoglycan; D,

Dermatophagoides pteronyssinus. (fd), gene expression as fold difference; n.d., no difference.

p-value from Kruskal-Wallis test. * $p \leq 0.05$, all other presented results are $p \leq 0.1$.

highest/lowest secretion or gene-expression in carriers with increasing number of the minor allele (SNP-HT-WT).

Table E4: Cytokine secretion [pg/ml] of Interleukin-6 (IL-6), IL-10, IL-13 and IL-17 secretion stratified for maternal atopy (raw data).

		Interleukin-6 (IL-6)											
SNP/LD-block	Genotype	CBMCs all				CBMCs of non-atopic mothers				CBMCs of atopic mothers			
Stimulation		1.Q	Med	3.Q	p(KW)	1.Q	Med	3.Q	p(KW)	1.Q	Med	3.Q	p(KW)
rs79309463	WT	1.40	4.85	16.11	0.81	1.03	4.14	17.52	0.54	2.11	6.05	13.46	0.42
	U	0.95	4.34	19.95		1.38	4.65	19.95		0.11	2.61	17.65	
	SNP	1.04	3.30	17.68		1.04	1.27	4.73		3.30	77.06	150.82	
	WT	18242.38	26486.50	42148.76	0.39	22104.71	30000.00	42148.76	0.69	15436.50	20403.87	36696.19	0.16
	PHA	23482.79	33866.08	63903.36		23482.79	34000.00	63903.36		24035.03	32735.12	179756.19	
	SNP	18482.63	28880.31	34000.00		15304.66	23121.63	785917.89		30000.00	32000.00	34000.00	
	WT	20309.37	30000.00	50221.17	0.81	23275.70	30611.84	43472.57	0.91	17930.83	25756.04	77294.78	0.42
	LpA	22561.28	31809.25	50753.75		22083.32	31809.25	46611.59		26088.10	40376.88	106334.38	
	SNP	14014.05	30000.00	40903.62		14014.05	28929.84	40903.62		30000.00	32000.00	34000.00	
	WT	18242.38	26486.50	42148.76	0.39	22104.71	30000.00	42148.76	0.69	15436.50	20403.87	36696.19	0.16
	Ppg	23482.79	33866.08	63903.36		23482.79	34000.00	63903.36		24035.03	32735.12	179756.19	
	SNP	18482.63	28880.31	34000.00		15304.66	23121.63	785917.89		30000.00	32000.00	34000.00	
	WT	23291.13	35139.62	72112.33	0.44	24000.00	33287.90	57577.60	0.89	22214.66	37586.58	126056.17	0.12
	D	26000.00	44638.02	70242.11		25584.63	36193.29	59131.17		44638.02	50329.90	264628.43	
	SNP	24673.54	30000.00	46119.71		24673.54	24813.83	46119.71		30000.00	30290.59	30581.17	
	WT	26715.38	34000.00	68640.01	0.17	30000.00	36408.79	63736.37	0.42	21272.06	31398.74	180000.00	0.31
	D+LpA	28102.88	44481.85	61347.93		19804.02	44481.85	56724.30		30000.00	51155.36	66461.44	
	SNP	20629.65	26859.63	30711.79		25197.26	26859.63	30711.79		10917.98	20458.99	30000.00	
rs10494879	WT	1.30	5.34	16.11	0.90	1.00	4.62	16.11	0.33	2.30	6.56	13.46	0.20
	U	1.32	4.03	19.95		1.92	4.41	37.56		0.51	4.03	6.21	
	SNP	1.04	3.86	14.05		0.62	3.48	7.85		3.30	29.09	150.82	
	WT	19606.03	29376.72	43217.76	0.75	20350.41	30000.00	34000.00	0.30	18357.59	25781.04	180000.00	0.08
	PHA	19430.15	31248.21	51063.29		25687.62	34773.18	89877.19		13226.81	17798.52	31866.08	
	SNP	22034.36	32000.00	819499.12		18482.63	27760.62	94923.08		30000.00	34000.00	1700000.00	
	WT	21067.52	30000.00	50712.47	0.83	21225.96	30000.00	36440.95	0.43	19878.25	28440.63	103121.52	0.67
	LpA	22561.28	33140.36	50753.75		23319.04	34000.00	46687.76		22501.18	28060.41	50753.75	
	SNP	22083.32	29534.58	40903.62		15035.74	28929.84	40903.62		30000.00	34000.00	151565.20	
	WT	19099.40	30000.00	73595.83	0.68	18373.04	30000.00	44929.41	0.30	19825.75	43876.20	180000.00	0.52
	Ppg	24000.00	33596.26	54099.31		24000.00	33998.43	72192.83		20938.71	31709.57	49541.87	
	SNP	17965.15	24184.79	41896.91		13796.57	22329.84	41896.91		30000.00	38424.04	1700000.00	
	WT	21138.18	31298.73	101497.10	0.59	17859.42	30000.00	73137.14	0.3	28425.35	39200.67	180000.00	0.96
	D	30000.00	40162.37	57577.60		30785.35	38281.00	57161.11		30000.00	44638.02	94862.37	
	SNP	24813.83	30581.17	49681.37		24673.54	35757.70	49681.37		30000.00	30581.17	264628.43	
	WT	26205.67	34000.00	160914.33	0.08	26205.67	34000.00	63736.37	0.17	24714.78	80627.68	951269.71	0.31
	D+LpA	30000.00	43920.78	58489.31		34000.00	45042.92	56724.30		30000.00	38818.49	64206.55	
	SNP	20629.65	26859.63	30711.79		22907.15	26859.63	30711.79		10917.98	20458.99	30000.00	
rs1800890 Block 1	WT	1.30	6.70	20.23	0.78	1.00	5.82	33.53	0.56	2.30	6.84	16.90	0.35
	U	1.38	4.23	15.37		2.39	4.65	19.95		0.51	4.03	11.55	
	SNP	1.04	3.30	14.05		0.62	1.92	14.05		3.30	6.05	150.82	

	PHA	WT	18981.81	30000.00	58845.50	0.61	22104.71	31949.80	43217.76	0.32	16402.77	24835.13	180000.0	0.63
		HT	17526.97	31738.07	44816.52		24027.50	34000.00	63903.36		11211.41	18070.06	33732.16	
		SNP	19636.44	26673.35	32000.00		18482.63	25586.08	30000.00		20790.24	30000.00	34000.00	
	LpA	WT	21825.66	30000.00	52421.21	0.41	22709.13	31274.92	50712.47	0.24	17930.83	26881.26	108110.8	0.97
		HT	23783.98	32845.90	46687.76		23783.98	33717.41	46687.76		18240.17	28060.41	50753.75	
		SNP	22083.32	28929.84	30000.00		15252.48	27003.87	30000.00		22501.18	30000.00	34000.00	
	Ppg	WT	21254.80	32000.00	87936.18	0.27	22792.32	30000.00	65704.50	0.25	16134.81	43876.20	180000.0	0.69
		HT	21188.74	33773.39	45292.03		24000.00	34000.00	47337.43		15062.94	30000.00	44984.43	
		SNP	21864.50	25205.23	30000.00		16304.65	22747.10	30000.00		26814.47	30000.00	38424.04	
	D	WT	24000.00	35139.62	101497.10	0.52	19756.20	30559.42	73137.14	0.40	28404.93	39200.67	180000.0	0.74
		HT	30000.00	42135.77	62000.89		33287.90	39989.33	62000.89		30000.00	44638.02	50329.90	
		SNP	24813.83	30000.00	46119.71		24743.69	27697.84	47900.54		30000.00	30581.17	40162.37	
	D+LpA	WT	27442.22	36573.66	110551.32	0.21	30000.00	39147.32	63940.19	0.35	22204.46	32447.51	302539.4	0.63
		HT	30174.99	41012.48	55612.19		32216.00	44481.85	55612.19		28102.88	34227.07	56013.31	
		SNP	20629.65	26859.63	39532.80		21768.40	26028.45	41527.46		10917.98	30000.00	39532.80	
rs1800871 Block 2	U	WT	1.35	4.23	14.87	0.99	1.35	4.23	17.52	0.95	1.30	4.13	11.24	0.74
		HT	1.03	6.39	20.23		1.38	8.17	19.95		0.33	6.21	20.23	
		SNP	1.22	6.84	16.90		1.00	2.21	29.53		4.03	10.15	15.18	
	PHA	WT	18362.51	30454.88	40248.38	0.83	26120.76	31949.80	43174.17	0.43	15436.50	20790.24	34000.0	0.30
		HT	20403.87	29376.72	70881.62		19606.03	26179.27	70881.62		21890.47	30000.00	41347.9	
		SNP	16402.77	26504.13	180000.00		10291.60	26504.13	30000.00		17380.18	99178.80	890000	
	LpA	WT	20875.81	30000.00	45080.17	0.59	22083.32	31498.95	40903.62	0.91	18240.17	28060.41	77294.7	0.55
		HT	24000.00	30000.00	46611.59		24902.59	30831.37	49516.40		23836.68	25756.04	30000.0	
		SNP	23275.70	38517.57	108110.81		23275.70	30000.00	56543.24		26660.41	73314.19	854055	
	Ppg	WT	17965.15	30000.00	44984.43	0.40	18373.04	29946.25	36317.88	0.38	15062.94	30000.00	81487.1	0.85
		HT	26000.00	33773.39	58335.73		25000.00	36673.66	65264.28		28905.51	33419.13	57348.8	
		SNP	21188.74	30000.00	178358.39		27839.08	30000.00	92578.54		14031.71	97246.60	889179	
	D	WT	25104.76	34000.00	48232.49	0.20	25104.76	34000.00	47783.07	0.53	24781.77	37170.15	61221.1	0.32
		HT	28404.93	45478.01	94862.37		26000.00	45478.01	73137.14		29202.47	46561.16	137431	
		SNP	35972.48	42449.48	180000.00		30000.00	39534.72	88816.63		39210.98	111224.7	890000	
	D+LpA	WT	26859.63	34000.00	47820.06	0.34	26859.63	34000.00	45156.94	0.41	15277.28	32447.51	64206.5	0.55
		HT	27225.09	48165.77	66461.44		30000.00	52410.75	63736.37		26205.76	30000.00	128807	
		SNP	22219.38	68145.81	1600000.00		26109.69	49072.91	124072.91		22204.46	1600000	1600000	
rs1878672 Block 3	U	WT	1.03	6.56	16.90	0.36	0.95	3.13	17.52	0.31	1.30	6.84	16.90	0.76
		HT	2.21	4.62	19.95		2.30	4.85	24.74		2.11	4.23	11.55	
		SNP	0.69	3.52	8.76		0.62	3.74	9.66		0.76	3.30	6.05	
	PHA	WT	20350.41	30309.54	180000.00	0.66	20350.41	34000.00	70881.62	0.93	18357.59	24835.13	180000	0.35
		HT	19606.03	30145.35	42148.76		21875.72	31248.21	44816.52		13226.81	21654.01	36543.0	
		SNP	18070.06	27760.62	35367.74		21713.08	28880.31	56835.42		16969.16	20790.24	33732.1	
	LpA	WT	22709.13	30525.45	50712.47	0.35	22142.55	31050.89	34000.00	0.21	23836.68	30000.00	108110	0.62
		HT	22882.00	33422.95	52084.85		23551.51	34000.00	52084.85		15815.70	27057.90	74442.9	
		SNP	18919.09	28495.13	37199.34		18477.25	28929.84	40398.67		22501.18	28060.41	34000.0	
	Ppg	WT	19813.92	30000.00	157306.74	0.60	18373.04	30000.00	65704.50	0.70	22870.20	57348.83	1600000	0.35
		HT	19825.75	30000.00	47337.43		24000.00	34000.00	58335.73		14128.01	29019.07	38824.8	
		SNP	18463.72	28407.24	43440.67		21864.50	25205.23	41896.91		15062.94	30000.00	44984.4	
		WT	21138.18	36185.99	180000.00		17143.97	30000.00	180000.00		28404.93	44173.43	180000	

D	HT	29306.33	36505.16	62000.89	0.78	29306.33	35461.17	62000.89	0.73	28425.35	39200.67	94862.3	0.51
	SNP	24673.54	34483.88	48379.03		24673.54	34193.29	48379.03		25121.76	35371.77	47483.9	
	WT	26205.67	34000.00	180000.00		26205.67	34000.00	160914.33		27225.09	128807.8	1600000	
	HT	27659.35	36852.20	56010.71		30000.00	41440.96	56010.71		20741.52	28829.68	57140.7	
D+LpA	SNP	24052.21	34407.98	47643.29	0.42	25197.26	38817.58	50215.20	0.95	12331.07	30349.97	39532.8	0.23
	WT	0.95	3.35	17.52		0.95	2.57	17.52		1.30	6.70	16.90	
	HT	2.39	4.62	16.11		2.42	4.85	18.03		2.11	4.23	11.55	
	SNP	0.76	4.45	14.05		0.83	4.24	11.86		0.76	4.45	29.09	
PHA	WT	19354.00	29376.72	38608.88	0.43	20350.41	30000.00	34000.00	0.40	18357.59	25321.96	180000	0.42
	HT	19606.03	31879.45	44816.52		21875.72	34000.00	44816.52		13226.81	21654.01	44078.6	
	SNP	15436.50	25586.08	34000.00		18482.63	27760.62	35367.74		15436.50	19430.15	33732.1	
	WT	20309.37	26343.22	34000.00		19574.22	27902.59	34000.00		23836.68	26318.65	38517.5	
LpA	HT	23260.88	34000.00	53026.12	0.13	26426.57	34000.00	52084.85	0.13	15815.70	32451.87	139066	0.71
	SNP	18240.17	28495.13	40398.67		18559.53	28999.50	40651.15		18240.17	27086.39	34000.0	
	WT	16304.65	26529.42	57348.83		16620.61	25919.54	34000.00		16134.81	27062.64	180000	
	HT	25448.95	34000.00	58335.73		25568.09	36199.29	58335.73		16362.96	31709.57	67714.8	
Ppg	SNP	13796.57	26009.85	44984.43	0.22	17830.54	24184.79	39644.44	0.13	12081.96	28407.24	44984.4	0.76
	WT	19756.20	30000.00	180000.00		17143.97	30000.00	101497.10		28404.93	42449.48	180000	
	HT	30000.00	36974.32	66121.50		30559.42	35930.33	59789.25		29212.68	40668.22	137431	
	SNP	22458.53	30290.59	47249.37		24673.54	30000.00	48379.03		20243.52	30581.17	44638.0	
D	WT	24722.24	34000.00	170457.17	0.38	26109.69	34000.00	112427.26	0.32	24714.78	80627.68	951269	0.59
	HT	27659.35	36852.20	56010.71		29677.13	39146.58	55255.39		26205.76	30000.00	66461.4	
	SNP	20629.65	30174.99	45042.92		22907.15	28785.71	45071.38		11624.53	30174.99	38818.4	
	WT	0.98	4.96	15.18		0.82	2.96	15.14		1.26	6.70	15.18	
rs3024496 Block 3 U	HT	2.39	5.07	37.56	0.31	1.92	5.07	37.56	0.54	4.03	5.53	189.53	0.48
	SNP	0.76	4.23	11.55		1.04	4.23	9.66		0.76	3.88	11.55	
	WT	18357.59	28753.44	43217.76		20350.41	30000.00	38348.00		18299.99	23362.80	180000	
	HT	21875.72	31879.45	44816.52		25195.97	31949.80	44816.52	0.50	15968.11	30000.00	41347.9	0.61
PHA	SNP	13781.59	24275.43	34683.87	0.27	12126.68	28880.31	70496.66		15436.50	19430.15	33732.1	
	WT	21825.66	30000.00	51203.77		18991.67	30000.00	34000.00		24796.36	34258.79	144055	
	HT	21359.02	32172.43	51029.50		23319.04	33434.81	51305.25		12077.10	23202.72	50753.7	0.33
	SNP	22083.32	30000.00	40903.62		22083.32	30000.00	40903.62	0.38	22501.18	29030.21	34903.7	
LpA	WT	18373.04	30000.00	178358.39	0.90	16936.56	29709.63	36199.29		24044.98	74451.13	890000	
	HT	24000.00	34000.00	58335.73		25568.09	34000.00	58335.73		12900.16	30000.00	43876.2	0.29
	SNP	15062.94	28038.14	44984.43		21864.50	25205.23	41896.91		15062.94	29019.07	44984.4	
	WT	20447.19	32986.24	180000.00		14294.18	28248.90	73487.56		32188.71	58142.88	180000	
D	HT	28865.84	34569.81	57161.11	0.96	29306.33	35461.17	57577.60	0.26	28425.35	31298.73	39200.6	0.23
	SNP	24813.83	38386.58	47480.18		24743.69	34193.29	47929.61		30000.00	40162.37	44638.0	
	WT	26205.67	34000.00	180000.00		24212.53	32000.00	112427.26		27225.09	128807.8	1600000	
	HT	27659.35	41440.96	58489.31		30000.00	43920.78	56724.30	0.88	15277.28	28829.68	66461.4	0.26
D+LpA	SNP	25197.26	38104.17	50215.20	0.67	25197.26	45042.92	52343.13		21165.54	34227.07	43676.4	
	WT	1.26	3.85	13.76		1.03	3.54	14.87		1.30	4.23	11.55	
	HT	1.89	5.56	33.55		2.39	5.07	29.53		0.20	6.05	189.53	0.83
	SNP	1.02	4.02	23.39		1.02	3.00	12.77		2.03	16.20	89.96	
rs3024498 Block 4 U	WT	18242.38	26504.13	41997.77	0.65	21799.76	30000.00	40172.89	0.54	15436.50	20403.87	46809.3	

PHA	HT	21875.72	33866.08	57310.05	0.40	24027.50	35457.05	82709.87	0.53	20790.24	30869.04	33732.1	0.36
	SNP	18482.63	28880.31	1544075.15		18482.63	26352.08	1544075.15		24035.03	32000.00	867000	
LpA	WT	20309.37	30000.00	50221.17	0.81	22709.13	30305.92	38509.66	0.33	17930.83	26496.81	98132.2	0.58
	HT	22882.00	32091.84	51029.50		26000.00	34000.00	51305.25		22501.18	24115.79	50753.7	
Ppg	SNP	16756.50	29464.92	37451.81	0.86	14524.90	23703.55	37169.22	0.36	29030.21	32000.00	92782.6	0.43
	WT	17965.15	29854.82	58335.73		21188.74	30000.00	44929.41		12900.16	28038.14	178358	
D	HT	26000.00	33773.39	54099.31	0.97	26000.00	34000.00	77831.48	0.79	26814.47	31709.57	33773.3	0.76
	SNP	18063.21	27602.62	67452.79		12565.36	23394.23	57563.19		34212.02	41704.24	872492	
D+LpA	WT	24000.00	35972.48	85217.51	0.73	26497.79	34000.00	73137.14	0.85	23291.13	37586.58	180000	0.73
	HT	30000.00	38386.58	48948.89		25886.79	34730.59	52320.24		40162.37	44638.02	48948.8	
	SNP	20467.16	30290.59	157479.17		16019.16	24743.69	823059.86		30290.59	40455.54	157479	
	WT	26205.67	34000.00	128807.84		29354.25	34000.00	63940.19		21738.26	31398.74	241269	
	HT	30000.00	39532.80	50215.20		24902.01	42680.87	51312.98		30000.00	38104.17	39532.8	
	SNP	25197.26	30355.90	52343.13		25197.26	30711.79	52343.13		10917.98	30000.00	64206.5	
Interleukin-10 (IL-10)													
rs79309463													
U	WT	0.05	0.13	0.21	0.03	0.10	0.15	0.21	<0.01	0.01	0.12	0.19	0.94
	HT	0.01	0.08	0.16		0.01	0.04	0.15		0.01	0.14	0.27	
PHA	SNP	0.01	0.01	0.15	0.94	0.01	0.01	0.15	0.86	0.01	0.11	0.22	0.91
	WT	38.53	96.70	200.09		38.53	98.03	200.09		33.54	86.44	207.86	
LpA	HT	35.93	95.86	202.10	0.93	35.93	118.45	219.98	0.28	48.39	82.72	143.02	0.32
	SNP	36.63	111.03	191.66		36.63	111.03	191.66		43.71	114.06	242.27	
Ppg	WT	106.43	179.33	235.16	0.39	128.49	184.28	269.06	0.83	93.42	146.46	227.34	0.20
	HT	88.90	167.01	323.57		92.54	182.75	343.31		82.85	144.66	190.59	
D	SNP	116.29	155.15	211.02	0.70	91.82	116.29	155.15	0.94	171.93	225.25	336.43	0.58
	WT	444.94	867.38	1359.40		581.27	916.10	1440.47		108.63	824.24	1257.93	
D+LpA	HT	402.97	744.83	1265.84	0.71	389.72	1036.17	1489.73	0.80	501.21	636.03	873.86	0.42
	SNP	832.40	1202.40	1214.46		745.07	1202.40	1208.37		921.97	1113.00	1358.25	
	WT	108.11	192.92	304.31		109.45	198.45	350.28		90.48	183.39	263.40	
	HT	78.93	160.71	298.93		77.65	192.70	349.77		80.13	136.23	213.95	
	SNP	128.07	210.37	251.71		155.92	219.38	251.71		92.22	153.14	362.95	
	WT	166.82	218.02	352.99		190.10	242.52	425.38		150.05	185.20	254.53	
	HT	138.30	282.50	426.04		198.90	303.26	464.88		82.97	237.56	374.68	
	SNP	185.41	240.42	439.51		185.41	232.80	302.33		240.42	339.97	439.51	
rs10494879													
U	WT	0.02	0.12	0.19	0.32	0.10	0.15	0.19	0.09	0.01	0.10	0.15	0.06
	HT	0.01	0.12	0.19		0.01	0.10	0.17		0.01	0.14	0.24	
PHA	SNP	0.01	0.16	0.31	0.55	0.01	0.15	0.24	0.82	0.09	0.22	0.34	0.61
	WT	30.20	96.38	162.15		38.53	104.30	188.80		25.72	82.18	146.19	
LpA	HT	51.72	97.62	219.98	0.78	49.98	99.21	219.98	0.27	52.44	94.10	195.56	0.49
	SNP	28.74	111.03	211.13		28.74	118.33	211.13		23.48	63.94	245.37	
Ppg	WT	104.27	169.91	222.41	0.98	121.54	179.33	221.78	0.56	93.42	147.40	223.82	0.19
	HT	94.44	180.16	308.84		128.16	197.99	343.31		82.85	139.59	233.95	
	SNP	114.30	168.82	248.48		91.82	157.57	248.48		127.86	196.74	336.43	
	WT	408.41	827.93	1322.99		408.41	824.23	1484.27		308.66	907.48	1310.32	
	HT	456.01	902.80	1265.84		518.22	1052.26	1396.66		383.30	578.06	966.42	
	SNP	511.83	745.07	1367.84		402.97	623.00	1367.84		690.43	921.97	1358.25	
	WT	106.52	181.11	280.17		104.11	161.72	280.17		113.98	192.92	304.31	

D	HT	84.17	160.71	284.64	0.94	113.05	198.61	349.77	0.68	57.76	124.38	235.18	0.20
	SNP	95.64	178.38	263.40		95.64	187.65	276.05		92.22	178.38	236.89	
	WT	160.01	217.64	352.99		190.10	242.52	376.98		116.66	181.64	352.99	
	HT	170.86	237.56	366.54		178.87	278.59	387.19		104.14	211.75	266.16	
D+LpA	SNP	185.41	255.86	483.95	0.55	185.41	255.86	483.95	0.90	240.42	339.97	439.51	0.39
	WT	0.02	0.12	0.19		0.10	0.15	0.21		0.01	0.10	0.16	
	HT	0.01	0.10	0.16		0.01	0.10	0.15		0.01	0.14	0.20	
	SNP	0.01	0.15	0.31		0.01	0.15	0.24		0.07	0.22	0.34	
PHA	WT	30.20	93.42	159.91	0.20	38.53	97.61	172.80	0.51	25.72	82.05	118.74	0.44
	HT	51.72	99.21	227.75		52.77	121.22	237.66		51.72	90.58	136.85	
	SNP	32.69	144.91	232.68		36.63	125.63	211.13		23.48	164.18	248.09	
	WT	103.95	169.71	223.12		125.23	180.34	222.41		91.90	146.46	223.82	
LpA	HT	92.07	184.28	307.45	0.85	94.07	192.45	323.57	0.59	82.85	152.21	236.37	0.68
	SNP	114.30	156.36	248.48		91.82	156.36	248.48		127.86	173.33	336.43	
	WT	444.94	835.63	1322.99		596.75	831.40	1440.47		88.31	867.38	1281.53	
	HT	456.01	962.13	1359.40		518.22	1131.46	1519.56		108.63	563.17	966.42	
Ppg	SNP	594.36	788.74	1367.84	0.98	402.97	684.04	1367.84	0.61	690.43	921.97	1358.25	0.25
	WT	106.52	172.69	280.17		107.32	164.14	293.23		90.48	181.11	271.33	
	HT	84.17	178.70	342.51		103.13	207.90	360.27		57.76	137.04	235.18	
	SNP	92.09	149.06	257.56		83.56	149.06	263.88		92.22	147.24	236.89	
D	WT	161.10	215.27	329.09	0.85	190.10	230.00	329.09	0.58	133.36	171.92	296.19	0.58
	HT	178.87	272.80	387.19		188.89	309.04	477.36		85.66	218.64	254.53	
	SNP	170.86	240.42	483.95		149.95	267.57	506.13		170.86	240.42	439.51	
	WT	0.01	0.13	0.21		0.01	0.12	0.21		0.02	0.14	0.21	
rs1800871 Block 2 U	HT	0.01	0.12	0.21	0.70	0.05	0.12	0.21	0.90	0.01	0.07	0.23	0.20
	SNP	0.01	0.12	0.16		0.06	0.14	0.17		0.01	0.06	0.12	
	WT	45.67	97.62	202.10		36.28	101.76	199.76		51.72	90.58	207.86	
	HT	26.68	95.80	172.80		26.68	97.61	172.80		25.42	89.71	172.63	
PHA	SNP	36.04	108.28	211.83	0.54	58.61	163.34	211.83	0.49	24.23	45.53	190.28	0.65
	WT	116.29	185.74	269.06		138.82	194.14	301.19		94.80	149.56	233.95	
	HT	92.07	146.93	248.80		92.07	153.41	289.42		88.83	146.93	228.93	
	SNP	101.00	170.57	305.13		112.22	170.57	282.19		88.26	158.62	337.46	
LpA	WT	450.48	833.06	1269.84	0.31	456.01	916.10	1421.78	0.20	383.30	770.88	1123.54	0.97
	HT	522.74	885.54	1359.40		627.52	1028.83	1484.27		230.94	824.24	1202.98	
	SNP	671.23	1302.26	2151.26		671.23	1135.77	1878.36		643.24	1632.84	2235.74	
	WT	88.54	165.63	284.64		97.92	166.55	298.93		85.80	164.70	263.40	
Ppg	HT	99.85	154.76	255.69	0.36	106.52	155.72	306.28	0.76	60.10	147.17	230.23	0.44
	SNP	134.77	242.66	360.27		107.64	242.66	360.27		201.71	289.19	370.06	
	WT	166.82	218.56	332.40		174.14	232.80	366.54		150.05	211.71	277.79	
	HT	152.48	255.18	433.36		198.90	280.24	519.56		112.39	181.64	237.56	
D	SNP	239.39	426.04	489.83	0.24	231.45	384.92	461.58	0.43	239.39	426.04	515.68	0.19
	WT	0.01	0.12	0.19		0.10	0.15	0.19		0.01	0.01	0.17	
	HT	0.01	0.11	0.16		0.01	0.10	0.15		0.02	0.15	0.24	
	SNP	0.01	0.15	0.24		0.01	0.15	0.24		0.01	0.16	0.23	
D+LpA	WT	33.54	96.38	159.91	0.23	48.03	104.30	188.80	0.04	25.72	66.68	95.21	0.16
	HT	0.01	0.12	0.19		0.10	0.15	0.19		0.01	0.01	0.17	
	SNP	0.01	0.11	0.16		0.01	0.10	0.15		0.02	0.15	0.24	
	WT	0.01	0.15	0.24		0.01	0.15	0.24		0.01	0.16	0.23	
rs1878672 Block 3 U	WT	33.54	96.38	159.91	0.25	48.03	104.30	188.80	0.04	25.72	66.68	95.21	0.16
	HT	0.01	0.12	0.19		0.10	0.15	0.19		0.01	0.01	0.17	
	SNP	0.01	0.11	0.16		0.01	0.10	0.15		0.02	0.15	0.24	
	WT	0.01	0.15	0.24		0.01	0.15	0.24		0.01	0.16	0.23	

PHA	HT	45.67	112.72	216.58	0.76	47.83	107.61	223.87	0.83	35.75	112.72	183.11	0.30
	SNP	30.25	89.65	211.13		26.18	78.52	201.10		51.72	94.10	248.09	
	WT	103.39	161.42	222.41		112.22	175.36	245.74		93.42	117.94	209.05	
LpA	HT	97.75	189.78	307.45	0.27	128.16	194.14	343.31	0.29	89.12	169.91	254.60	0.72
	SNP	96.88	156.36	248.05		114.30	166.68	248.48		85.86	143.77	247.62	
	WT	299.35	826.77	1310.32		243.02	821.51	1375.06		550.32	907.48	1310.32	
Ppg	HT	509.61	990.73	1455.76	0.56	652.04	1052.26	1519.56	0.19	88.31	575.84	1162.93	0.43
	SNP	416.70	757.23	1205.39		402.97	705.01	1273.84		511.83	832.40	1115.36	
	WT	97.92	145.27	244.80		100.05	134.77	298.93		80.90	147.17	224.58	
D	HT	113.37	230.23	349.77	0.14	138.14	230.41	408.35	0.18	61.87	230.23	271.33	0.73
	SNP	85.80	159.09	251.71		77.65	202.24	276.05		85.80	149.75	210.37	
	WT	126.39	205.62	366.54		166.82	241.61	366.54		114.69	170.83	332.72	
D+LpA	HT	198.90	272.80	464.88	0.19	198.90	280.24	489.83	0.37	183.52	228.06	303.76	0.71
	SNP	122.61	225.72	302.33		185.41	232.80	302.33		122.61	218.64	277.79	
rs1800893													
Block 3	WT	0.09	0.15	0.19	0.11	0.10	0.15	0.19	<0.01	0.01	0.06	0.17	0.30
	HT	0.01	0.11	0.16		0.01	0.10	0.15		0.02	0.14	0.24	
	SNP	0.01	0.15	0.24		0.01	0.18	0.24		0.02	0.13	0.21	
PHA	WT	47.23	97.61	183.11	0.97	59.63	109.67	188.81	0.79	47.23	82.30	108.66	0.55
	HT	49.98	112.72	216.58		51.38	110.37	232.71		35.75	112.72	146.19	
	SNP	33.09	89.65	206.62		26.82	88.71	200.09		51.72	90.58	248.09	
LpA	WT	104.27	169.12	223.82	0.46	118.24	178.13	279.24	0.60	94.80	132.20	209.05	0.78
	HT	126.32	189.08	284.48		132.43	194.14	323.57		89.12	167.01	254.60	
	SNP	91.82	149.91	248.48		91.82	162.13	287.47		88.88	142.38	234.30	
Ppg	WT	356.69	825.50	1322.99	0.59	328.02	821.51	1380.66	0.26	550.32	872.51	1281.53	0.52
	HT	501.11	990.73	1455.76		652.08	1052.26	1519.56		108.63	575.84	1162.93	
	SNP	430.43	800.89	1208.37		430.43	970.83	1367.84		447.57	800.89	1081.47	
D	WT	97.92	143.37	244.80	0.10	100.05	133.01	244.80	0.14	80.90	147.17	224.58	0.66
	HT	113.37	231.09	349.77		142.33	233.97	360.27		61.87	230.66	278.51	
	SNP	84.17	142.19	263.40		74.57	149.06	357.63		85.80	140.41	210.37	
D+LpA	WT	121.53	204.66	376.98	0.10	166.82	217.64	336.51	0.32	112.72	181.64	426.04	0.64
	HT	204.85	278.59	464.88		205.90	291.75	483.88		204.85	237.56	352.99	
	SNP	118.55	225.72	370.92		114.48	260.00	483.95		122.61	194.75	277.79	
rs3024496													
Block 3	WT	0.06	0.15	0.19	0.09	0.10	0.15	0.19	<0.01	0.01	0.11	0.17	0.31
	HT	0.01	0.10	0.16		0.01	0.09	0.14		0.05	0.15	0.24	
	SNP	0.01	0.15	0.24		0.01	0.15	0.24		0.01	0.15	0.22	
PHA	WT	33.54	96.38	162.15	0.70	59.63	109.67	200.34	0.68	23.62	61.62	94.32	0.11
	HT	51.38	118.60	212.22		49.98	96.76	203.29		53.16	130.66	216.58	
	SNP	30.25	90.58	211.13		25.53	62.67	202.10		51.72	97.62	248.09	
LpA	WT	98.77	155.23	222.41	0.14	115.85	175.36	269.06	0.29	93.42	113.12	189.69	0.40
	HT	128.16	194.14	307.45		132.43	193.30	323.57		89.12	206.15	258.41	
	SNP	85.86	155.15	247.62		66.08	157.57	287.47		93.90	144.22	234.30	
Ppg	WT	186.68	824.23	1310.32	0.38	186.68	818.75	1322.99	0.21	550.32	897.21	1281.53	0.72
	HT	522.74	1041.51	1421.78		652.08	1051.50	1421.78		108.63	738.64	1242.52	
	SNP	430.43	769.38	1208.37		402.97	745.07	1367.84		530.05	800.89	1081.47	
D	WT	90.48	135.24	242.66	0.05	98.99	133.01	288.86	0.19	80.47	143.37	206.08	0.28
	HT	131.30	230.90	349.77		138.14	230.41	346.14		81.32	235.88	381.52	

D+LpA	SNP	84.99	157.51	257.56	0.30	77.65	155.92	276.05	0.69	85.80	159.09	240.13	0.74
	WT	126.39	203.70	417.44		166.82	241.61	417.44		114.69	170.83	332.72	
	HT	193.23	272.80	387.19		198.90	278.59	387.19		162.19	236.55	352.99	
	SNP	122.61	232.80	302.33		114.48	255.86	489.83		122.61	211.75	277.79	
rs3024498													
Block 4 U	WT	0.02	0.12	0.19	0.15	0.10	0.14	0.19	0.03	0.01	0.12	0.19	0.66
	HT	0.01	0.10	0.21		0.01	0.08	0.15		0.01	0.14	0.28	
	SNP	0.01	0.01	0.16		0.01	0.01	0.15		0.01	0.09	0.21	
PHA	WT	39.27	98.03	200.34	0.85	48.03	106.99	200.34	0.81	33.54	85.99	162.15	0.98
	HT	35.75	94.09	203.29		32.34	95.43	202.70		35.75	90.58	248.09	
	SNP	26.82	73.33	191.66		23.92	73.83	194.54		48.39	73.33	164.18	
LpA	WT	103.51	177.18	231.86	0.98	121.54	183.57	258.77	0.86	94.11	146.93	225.58	0.68
	HT	92.54	167.01	323.57		94.07	188.08	343.31		84.36	144.22	244.28	
	SNP	116.29	172.87	247.62		104.06	150.72	260.63		140.98	196.74	247.62	
Ppg	WT	428.26	833.71	1367.84	0.93	501.00	829.08	1484.27	0.84	197.47	867.38	1269.73	0.23
	HT	407.45	868.44	1265.65		456.01	1131.46	1519.56		383.30	636.03	873.86	
	SNP	511.83	988.98	1214.46		360.13	973.74	1237.11		832.40	988.98	1214.46	
D	WT	103.62	188.05	280.77	0.65	106.52	166.55	281.37	0.51	80.90	192.92	271.33	0.43
	HT	78.29	159.14	328.03		77.65	179.77	360.27		78.93	124.38	164.70	
	SNP	128.07	206.31	276.05		179.08	235.55	309.28		88.54	146.79	210.37	
D+LpA	WT	161.10	218.10	385.22	0.70	182.92	242.52	425.38	0.71	136.33	196.80	303.76	0.95
	HT	174.14	277.79	464.88		198.90	287.20	489.83		85.66	204.21	277.79	
	SNP	185.41	236.61	366.54		185.41	232.80	366.54		82.97	240.42	439.51	
Interleukin-13 (IL-13)													
rs79309463													
U	WT	0.23	0.46	0.79	0.06	0.25	0.52	0.85	0.01	0.13	0.38	0.72	0.89
	HT	0.13	0.33	0.60		0.13	0.30	0.59		0.21	0.40	0.65	
	SNP	0.27	0.81	1.35		0.79	0.83	1.35		0.14	0.54	1.93	
PHA	WT	28.95	242.51	1745.74	0.55	12.53	227.31	1284.73	0.74	51.17	378.62	2219.78	0.65
	HT	30.20	289.57	2381.57		18.70	240.32	2356.14		70.41	466.25	2699.96	
	SNP	109.65	122.13	212.57		109.65	113.00	212.57		77.42	145.56	481.77	
LpA	WT	1.92	4.99	13.14	0.39	2.18	6.18	13.51	0.21	1.72	3.97	12.99	0.89
	HT	1.69	5.52	12.15		1.83	6.55	12.15		1.29	2.70	10.46	
	SNP	1.18	3.84	4.83		1.01	2.38	3.84		2.65	4.88	9.91	
Ppg	WT	14.91	25.50	59.34	0.75	13.92	28.27	61.67	0.25	14.91	25.45	43.51	0.58
	HT	5.87	24.03	70.70		4.71	24.05	66.79		7.33	17.63	70.70	
	SNP	13.83	31.38	34.73		4.80	13.83	19.90		31.96	33.64	42.89	
D	WT	4.15	10.11	20.59	0.29	4.23	9.51	22.83	0.10	3.40	10.22	18.00	1.00
	HT	1.98	11.71	21.48		1.98	11.71	18.43		2.63	12.83	27.78	
	SNP	1.77	5.14	15.01		1.22	2.42	5.14		4.28	10.90	32.67	
D+LpA	WT	2.99	7.01	17.90	0.12	2.57	5.97	17.53	0.20	5.38	9.99	18.76	0.41
	HT	4.43	10.51	23.29		5.48	11.77	19.27		4.43	5.08	35.86	
	SNP	1.56	2.85	6.15		2.56	2.85	4.96		1.56	3.86	6.15	
rs10494879													
U	WT	0.18	0.49	0.76	0.40	0.29	0.52	0.81	0.28	0.11	0.29	0.57	0.46
	HT	0.18	0.38	0.65		0.18	0.35	0.59		0.21	0.39	0.70	
	SNP	0.24	0.41	1.35		0.21	0.41	1.35		0.30	0.46	1.73	
	WT	12.53	217.28	1504.77		11.57	252.32	1704.72		41.08	212.85	1297.49	

PHA	HT	29.80	360.07	2699.96	0.43	10.53	200.23	1695.38	0.90	115.73	1534.96	4403.30	0.03
	SNP	32.71	187.31	481.05		109.65	219.94	868.63		30.20	122.13	187.31	
	WT	1.77	5.20	13.53		1.85	7.67	14.56		1.56	4.52	10.60	
LpA	HT	2.26	4.49	13.13	0.19	2.32	5.24	9.38	0.31	1.91	3.18	13.13	0.54
	SNP	1.01	3.84	8.52		1.01	3.84	10.38		1.06	2.70	5.86	
	WT	14.93	25.45	59.99		15.48	25.39	67.23		14.91	25.50	51.01	
Ppg	HT	9.51	26.20	66.79	0.28	12.36	28.42	61.29	0.33	7.33	25.49	70.70	0.82
	SNP	3.79	19.90	37.02		2.35	19.44	37.02		7.16	31.96	39.12	
	WT	3.40	10.17	26.31		3.42	16.50	31.78		3.37	10.08	16.81	
D	HT	4.70	11.84	20.59	0.03	6.01	11.71	18.61	0.06	4.18	15.85	28.76	0.23
	SNP	1.63	7.40	9.97		1.63	6.57	9.97		1.55	7.47	11.73	
	WT	2.76	7.76	18.76		2.21	10.54	19.48		2.99	6.94	15.78	
D+LpA	HT	4.49	7.72	19.91	0.45	4.25	7.70	15.89	0.76	4.49	8.56	37.06	0.49
	SNP	2.56	6.15	11.97		2.85	6.16	11.97		1.56	3.86	6.15	
rs1800890													
Block 1	WT	0.21	0.50	0.81	0.20	0.30	0.52	0.85	0.09	0.11	0.31	0.65	0.67
	HT	0.16	0.36	0.59		0.16	0.33	0.58		0.21	0.39	0.65	
	SNP	0.24	0.47	0.83		0.21	0.51	1.35		0.30	0.46	0.76	
PHA	WT	23.18	217.28	1297.49	0.70	12.53	253.31	1284.73	0.94	41.08	208.42	1297.49	0.23
	HT	26.86	336.52	2824.53		6.51	153.61	2340.36		76.94	1745.74	3182.94	
	SNP	111.33	202.41	490.00		113.00	227.31	481.05		32.71	168.99	794.55	
LpA	WT	1.92	5.21	13.14	0.36	2.24	7.59	13.53	0.25	1.61	4.52	10.60	0.98
	HT	1.83	4.34	12.53		2.05	5.10	12.43		1.72	2.81	12.53	
	SNP	1.18	3.98	8.52		1.01	3.11	8.52		1.24	4.88	10.12	
Ppg	WT	14.93	25.45	62.05	0.28	15.49	26.27	70.15	0.05	14.91	25.45	51.01	0.61
	HT	7.57	25.49	60.42		14.67	31.67	66.79		5.87	18.60	54.71	
	SNP	4.80	19.67	37.02		2.35	11.34	22.53		20.96	33.64	47.28	
D	WT	3.37	10.17	25.07	0.18	3.32	13.37	28.24	0.05	3.37	10.10	16.81	0.97
	HT	4.43	11.67	19.84		7.06	11.67	17.64		2.60	13.45	26.05	
	SNP	1.70	7.40	12.49		1.56	3.78	9.03		4.28	8.30	32.67	
D+LpA	WT	2.75	7.35	17.72	0.55	2.21	6.77	18.64	0.43	4.19	7.58	16.66	0.85
	HT	4.49	7.72	14.34		4.58	8.68	15.14		4.43	5.08	10.05	
	SNP	1.56	4.96	12.92		1.83	3.91	9.54		1.56	6.15	148.37	
rs1800871													
Block 2	WT	0.24	0.43	0.77	0.28	0.21	0.41	0.71	0.57	0.25	0.44	0.81	0.13
	HT	0.11	0.36	0.65		0.18	0.38	0.84		0.01	0.22	0.58	
	SNP	0.29	0.58	0.83		0.31	0.70	0.99		0.22	0.43	0.69	
PHA	WT	32.71	430.57	2623.28	0.08	22.56	271.62	2230.84	0.27	70.41	794.55	3182.94	0.29
	HT	10.53	122.90	1170.14		5.40	70.95	1170.14		42.19	212.85	1044.13	
	SNP	56.12	199.08	521.59		56.12	173.65	502.98		64.97	252.80	2458.15	
LpA	WT	1.91	4.17	10.38	0.98	2.24	4.83	11.62	0.93	1.61	3.22	9.25	0.77
	HT	1.77	6.22	12.99		1.77	6.22	13.53		1.93	6.15	12.76	
	SNP	1.81	4.01	14.21		2.02	5.21	14.29		1.81	3.72	9.81	
Ppg	WT	9.31	26.68	59.88	1.00	9.51	25.96	62.05	0.97	6.64	30.46	54.71	0.99
	HT	12.36	24.05	59.99		9.95	24.05	59.99		13.44	22.70	48.94	
	SNP	12.71	30.68	45.49		12.71	24.67	53.32		16.36	35.09	45.49	
D	WT	3.32	10.17	19.59	0.20	3.11	10.23	19.22	0.36	3.92	10.12	20.59	0.41
	HT	4.30	15.35	31.78		4.30	12.93	38.53		3.37	16.17	26.31	

D+LpA	SNP	3.19	5.98	14.56	0.77	2.70	8.38	16.50	0.84	3.25	4.61	10.23	0.87
	WT	2.85	8.36	16.52		2.56	8.68	16.52		4.43	7.64	18.76	
	HT	2.99	6.92	21.60		2.73	6.35	17.90		4.55	6.94	21.60	
	SNP	2.61	6.12	15.78		1.93	5.38	13.67		2.61	6.12	15.78	
rs1878672 Block 3 U	WT	0.13	0.38	0.68	0.65	0.25	0.45	0.76	1.00	0.10	0.18	0.57	0.30
	HT	0.24	0.44	0.77		0.23	0.42	0.82		0.25	0.46	0.77	
	SNP	0.20	0.37	0.80		0.21	0.36	0.83		0.04	0.38	0.79	
	WT	31.69	252.32	1704.72	0.77	12.74	271.18	1704.72	0.98	51.17	224.99	1297.49	0.76
	HT	20.72	158.33	1972.92		10.53	162.15	2330.70		33.70	154.51	1745.74	
	SNP	109.65	234.82	1206.75		111.33	221.87	683.79		70.41	630.40	2873.23	
	WT	1.93	5.20	13.53	0.32	2.09	7.45	14.56	0.18	1.56	4.52	10.60	0.99
	HT	1.91	4.95	11.62		2.26	5.71	11.62		1.61	3.22	12.53	
	SNP	1.31	3.31	9.53		1.33	3.16	8.68		1.29	3.45	14.17	
	WT	14.93	27.15	65.84	0.20	11.55	26.27	76.41	0.08	16.10	27.40	51.01	0.59
	HT	10.94	25.10	59.88		15.48	33.16	59.34		6.64	16.58	60.42	
	SNP	4.25	21.22	43.08		4.71	13.83	25.71		3.79	32.54	50.36	
	WT	3.42	10.05	26.31	0.18	3.42	10.23	31.78	0.03	3.37	8.93	16.81	0.98
	HT	4.20	11.22	20.03		6.89	11.93	20.00		3.32	10.11	20.59	
	SNP	1.77	8.14	15.01		1.49	5.14	11.67		3.92	10.17	27.26	
	WT	2.99	7.76	17.15	0.49	2.01	7.76	17.90	0.35	5.75	7.58	14.59	0.82
	HT	3.34	7.88	21.34		4.25	9.60	21.34		1.93	5.81	27.31	
	SNP	2.56	5.62	11.97		2.56	4.96	11.97		4.43	6.15	11.76	
rs1800893 Block 3 U	WT	0.14	0.42	0.62	0.86	0.29	0.51	0.76	0.64	0.10	0.16	0.57	0.13
	HT	0.23	0.41	0.77		0.18	0.39	0.74		0.25	0.46	1.03	
	SNP	0.18	0.33	0.79		0.21	0.34	0.83		0.15	0.33	0.70	
	WT	31.69	235.50	1284.73	0.69	12.53	252.32	1080.30	0.70	51.17	217.28	1297.49	0.67
	HT	25.02	271.93	2481.82		18.25	383.46	2623.28		33.70	154.51	1745.74	
	SNP	90.03	234.82	1659.92		109.65	212.57	481.05		70.41	794.55	3182.94	
	WT	1.93	5.11	13.99	0.22	2.23	6.49	14.69	0.11	1.56	4.77	12.53	0.94
	HT	2.24	5.21	10.46		2.32	6.37	11.62		1.61	3.22	10.46	
	SNP	1.29	3.08	8.52		1.01	2.18	8.52		1.84	3.78	11.22	
	WT	15.62	25.45	56.07	0.08	12.79	25.21	64.64	0.01	16.10	26.45	39.97	0.82
	HT	10.94	29.52	67.76		15.48	41.03	66.99		6.64	18.40	70.70	
	SNP	3.79	19.67	37.02		2.35	11.34	24.02		7.16	31.96	46.94	
	WT	3.42	11.13	27.21	0.12	3.42	12.39	31.78	0.02	5.90	11.13	16.81	0.99
	HT	4.30	12.63	20.06		6.98	12.63	19.72		3.32	12.91	24.84	
	SNP	1.63	8.14	15.01		1.37	3.78	10.82		3.92	10.22	27.26	
	WT	2.80	7.40	17.53	0.29	2.01	7.03	17.90	0.13	5.38	8.21	15.78	0.97
	HT	4.24	11.24	21.34		4.58	11.97	19.38		2.76	7.07	35.86	
	SNP	2.06	5.62	12.34		1.43	3.91	8.36		4.43	8.10	17.54	
rs3024496 Block 3 U	WT	0.15	0.44	0.76	0.99	0.27	0.51	0.81	0.53	0.11	0.29	0.57	0.37
	HT	0.23	0.39	0.68		0.18	0.37	0.68		0.25	0.50	0.77	
	SNP	0.21	0.38	0.79		0.21	0.36	0.83		0.13	0.39	0.75	
	WT	31.69	232.69	1297.49	0.88	11.57	252.32	1704.72	0.86	46.13	212.85	1155.04	0.58
	HT	10.53	162.15	2330.70		10.53	208.22	2330.70		33.70	124.66	1504.77	

	LpA	SNP	70.41	227.31	938.27	0.18	46.52	202.41	481.05	0.07	70.41	794.55	2873.23	0.85
		WT	1.93	5.02	13.99		2.24	6.49	14.78		1.91	4.52	10.60	
		HT	2.01	5.08	11.04		2.32	6.55	11.62		0.77	3.08	10.46	
	Ppg	SNP	1.18	2.70	10.38	0.09	0.61	1.98	10.38	0.01	1.84	3.71	11.22	0.61
		WT	12.43	25.50	62.05		8.22	25.21	67.23		16.10	27.40	51.01	
		HT	14.67	27.36	66.79		17.68	38.84	66.79		6.64	16.58	60.42	
	D	SNP	3.79	19.90	37.02	0.12	2.35	8.84	24.02	0.01	7.16	31.96	46.94	0.96
		WT	3.37	8.93	27.21		3.32	9.34	35.16		3.37	8.93	16.81	
		HT	4.43	11.93	20.00		7.06	13.32	20.00		1.99	10.10	20.59	
	D+LpA	SNP	1.56	8.30	15.27	0.29	1.24	2.42	11.29	0.09	3.92	10.22	27.26	0.50
		WT	2.99	7.03	17.15		2.01	7.03	17.90		5.75	7.58	14.59	
		HT	3.92	11.04	19.38		5.17	12.85	21.34		1.10	3.66	18.76	
		SNP	1.56	5.08	11.76		1.10	2.85	11.97		4.43	6.61	11.76	
rs3024498 Block 4														
	U	WT	0.21	0.40	0.73	0.19	0.24	0.45	0.76	0.25	0.11	0.38	0.65	0.62
		HT	0.13	0.39	0.68		0.13	0.36	0.74		0.11	0.42	0.65	
		SNP	0.27	0.80	1.35		0.26	0.81	1.31		0.27	0.57	2.64	
	PHA	WT	23.18	238.31	2105.56	0.71	12.53	245.32	2121.31	0.83	51.17	232.69	1745.74	0.69
		HT	46.52	271.93	1824.52		10.53	242.33	1695.38		70.41	466.25	2699.96	
		SNP	32.71	145.56	288.95		69.73	162.79	252.69		32.71	145.56	794.55	
	LpA	WT	1.84	4.99	13.40	0.22	1.85	6.20	13.76	0.22	1.82	3.97	11.80	0.86
		HT	1.91	6.68	12.34		2.12	6.68	11.89		1.45	4.99	12.83	
		SNP	1.18	2.80	4.83		1.35	2.77	4.34		1.18	3.28	5.65	
	Ppg	WT	12.43	25.49	57.58	0.72	12.36	26.20	61.29	0.28	13.67	25.45	43.08	0.64
		HT	8.34	24.05	68.75		9.51	24.07	66.79		7.33	17.63	70.70	
		SNP	4.80	25.64	37.02		3.47	11.56	28.46		31.38	33.64	51.04	
	D	WT	4.20	10.03	20.33	0.06	4.96	9.86	20.59	0.07	3.37	10.11	18.00	0.47
		HT	2.73	15.35	24.84		2.73	13.45	19.22		4.43	15.85	28.30	
		SNP	1.24	4.04	11.75		1.23	3.29	8.45		1.77	5.36	15.01	
	D+LpA	WT	2.99	7.05	17.53	0.13	2.70	6.98	17.53	0.32	4.19	7.64	17.27	0.36
		HT	3.33	10.28	25.96		2.73	11.24	23.29		4.55	7.57	35.86	
		SNP	2.56	3.98	6.15		2.56	3.52	11.57		1.56	4.43	6.15	
Interleukin-17 (IL-17)														
rs79309463														
	U	WT	0.01	0.44	0.65	<0.01	0.01	0.44	0.65	<0.01	0.01	0.44	0.66	0.37
		HT	0.01	0.01	0.47		0.01	0.02	0.46		0.01	0.01	0.50	
		SNP	0.32	0.69	1.37		0.69	0.72	1.41		0.17	0.49	1.01	
	PHA	WT	0.01	0.32	0.95	0.44	0.01	0.22	0.81	0.39	0.01	0.47	1.12	0.11
		HT	0.01	0.07	0.84		0.01	0.01	1.07		0.01	0.12	0.33	
		SNP	0.01	0.23	0.84		0.23	0.84	1.56		0.01	0.02	0.17	
	LpA	WT	0.53	2.69	5.46	0.52	0.65	3.57	5.66	0.40	0.47	1.71	4.20	0.89
		HT	0.43	1.82	5.28		0.46	1.96	3.43		0.43	1.26	6.51	
		SNP	0.65	1.64	2.44		0.06	2.24	13.36		0.75	1.24	2.04	
	Ppg	WT	0.98	2.94	9.41	0.77	1.12	2.79	11.14	0.72	0.93	3.02	9.10	0.99
		HT	0.80	3.07	10.72		1.35	3.00	5.77		0.74	3.21	10.90	
		SNP	0.84	2.44	4.03		0.54	0.84	7.15		1.73	3.16	3.95	
	D	WT	0.56	2.78	7.52	0.79	0.56	2.79	7.33	0.78	0.84	2.78	8.47	0.77
		HT	0.60	2.66	7.31		0.01	2.74	6.08		1.01	2.62	9.08	

D+LpA	SNP	0.23	0.84	6.12	0.48	0.23	0.84	6.12	0.65	0.33	2.63	6.10	0.63
	WT	0.46	2.66	6.93		0.47	2.66	6.65		0.46	2.91	8.25	
	HT	1.21	3.98	9.15		0.84	3.96	6.73		1.57	4.39	13.46	
	SNP	0.54	1.27	6.93		0.54	1.27	6.93		0.65	1.74	2.82	
rs10494879													
U	WT	0.01	0.31	0.63	0.11	0.01	0.40	0.61	0.24	0.01	0.01	0.74	0.35
	HT	0.01	0.13	0.58		0.01	0.13	0.54		0.01	0.10	0.60	
	SNP	0.01	0.60	0.71		0.01	0.60	0.72		0.17	0.60	0.65	
PHA	WT	0.01	0.28	0.98	0.94	0.01	0.33	0.93	0.99	0.01	0.23	0.98	0.78
	HT	0.01	0.22	0.84		0.01	0.32	0.84		0.01	0.15	0.88	
	SNP	0.01	0.22	0.84		0.01	0.23	1.18		0.01	0.02	0.33	
LpA	WT	0.50	3.03	6.49	0.24	1.13	3.86	6.53	0.32	0.46	1.42	5.12	0.16
	HT	0.46	2.06	4.87		0.46	2.22	4.76		0.56	1.86	10.18	
	SNP	0.06	0.84	5.42		0.06	2.10	8.03		0.24	0.56	1.24	
Ppg	WT	0.98	2.79	9.41	0.07	1.13	2.97	11.95	0.33	0.93	2.22	9.10	0.11
	HT	1.35	3.50	10.98		1.35	3.00	10.40		0.96	5.79	11.39	
	SNP	0.22	1.10	4.03		0.01	1.65	7.15		0.48	0.95	3.16	
D	WT	0.72	2.73	7.54	0.11	0.56	2.90	7.54	0.58	0.84	1.97	10.51	0.06
	HT	0.98	2.97	7.64		0.54	2.97	5.35		1.65	3.72	9.08	
	SNP	0.22	0.79	4.61		0.22	1.41	6.12		0.17	0.63	2.81	
D+LpA	WT	0.46	1.69	6.93	0.33	0.47	2.66	6.81	0.89	0.46	1.27	7.06	0.21
	HT	0.98	4.00	8.25		0.84	3.73	6.51		2.39	6.73	12.81	
	SNP	0.65	1.68	6.93		1.27	1.68	6.93		0.65	1.74	2.82	
rs1800890													
Block 1 U	WT	0.01	0.47	0.65	0.01	0.01	0.47	0.65	0.02	0.01	0.44	0.67	0.35
	HT	0.01	0.02	0.50		0.01	0.02	0.47		0.01	0.10	0.60	
	SNP	0.17	0.60	0.71		0.17	0.64	0.71		0.17	0.60	0.69	
PHA	WT	0.01	0.33	0.93	0.63	0.01	0.27	0.81	0.90	0.01	0.40	1.01	0.62
	HT	0.01	0.11	0.84		0.01	0.17	0.84		0.01	0.09	0.93	
	SNP	0.01	0.28	1.01		0.01	0.23	0.84		0.01	0.32	1.52	
LpA	WT	0.61	2.93	5.98	0.26	1.13	3.75	6.47	0.22	0.47	1.71	5.12	0.75
	HT	0.19	1.91	4.28		0.21	2.14	4.30		0.19	1.68	4.28	
	SNP	0.47	1.24	5.42		0.06	1.94	8.03		0.47	0.75	2.04	
Ppg	WT	0.98	2.94	9.24	0.31	0.97	2.94	10.20	0.35	0.98	2.76	9.10	0.84
	HT	0.96	3.17	10.72		1.35	3.07	11.01		0.74	3.26	7.88	
	SNP	0.74	1.38	4.03		0.54	1.38	7.15		0.81	1.73	3.95	
D	WT	0.72	2.73	7.54	0.44	0.56	2.79	7.53	0.57	0.93	2.54	8.47	0.71
	HT	0.56	2.74	7.64		0.54	3.27	6.88		0.81	2.62	8.22	
	SNP	0.28	0.92	5.37		0.12	1.41	4.67		0.46	0.83	6.10	
D+LpA	WT	0.46	1.97	6.46	0.52	0.47	2.66	6.46	0.68	0.46	1.48	6.17	0.60
	HT	0.84	3.96	7.93		0.67	3.85	7.96		1.57	4.39	7.93	
	SNP	0.54	1.68	10.37		0.28	1.48	8.65		0.65	2.82	81.34	
rs1800871													
Block 2 U	WT	0.01	0.23	0.65	0.73	0.01	0.22	0.65	0.92	0.01	0.32	0.65	0.38
	HT	0.01	0.19	0.60		0.01	0.22	0.81		0.01	0.10	0.57	
	SNP	0.06	0.47	0.61		0.06	0.45	0.52		0.28	0.69	0.98	
PHA	WT	0.01	0.23	1.04	0.57	0.01	0.28	1.02	0.24	0.01	0.18	1.04	0.64
	HT	0.01	0.23	0.80		0.01	0.28	0.81		0.01	0.23	0.54	

	LpA	SNP	0.01	0.06	0.54	0.13	0.01	0.01	0.27	0.16	0.24	0.73	1.05	0.87
		WT	0.46	2.08	4.87		0.46	2.24	5.49		0.47	1.71	4.17	
		HT	1.13	2.80	7.06		1.13	3.03	6.49		0.24	1.34	10.40	
	Ppg	SNP	0.10	1.21	2.49	0.60	0.10	0.64	2.83	0.81	0.71	1.42	2.37	0.81
		WT	0.90	3.17	9.93		0.84	2.91	10.98		0.93	3.50	8.31	
		HT	0.87	2.97	10.72		1.30	2.97	9.41		0.38	2.62	16.30	
	D	SNP	0.98	1.86	4.18	0.18	0.48	2.25	5.78	0.21	1.20	1.47	2.62	0.67
		WT	0.60	2.66	7.31		0.47	2.74	6.12		0.93	2.57	7.64	
		HT	0.60	2.73	12.15		0.56	3.21	12.54		0.60	2.66	12.15	
	D+LpA	SNP	0.01	0.56	4.44	0.47	0.01	0.56	7.13	0.62	0.35	2.02	4.01	0.41
		WT	0.65	3.73	7.93		0.54	3.73	6.73		0.65	4.40	8.56	
		HT	0.11	2.71	10.72		0.12	3.57	12.93		0.01	1.57	7.06	
rs1878672 Block 3	U	SNP	0.22	1.27	3.57	0.89	0.12	1.27	4.63	0.60	1.13	1.27	3.57	0.85
		WT	0.01	0.34	0.63		0.01	0.40	0.61		0.01	0.01	0.74	
		HT	0.01	0.23	0.60		0.01	0.11	0.60		0.01	0.32	0.60	
	PHA	SNP	0.01	0.20	0.65	0.75	0.01	0.17	0.67	0.73	0.01	0.32	0.65	0.78
		WT	0.01	0.28	1.11		0.01	0.33	1.17		0.01	0.23	0.54	
		HT	0.01	0.32	0.81		0.01	0.23	0.80		0.01	0.54	0.93	
	LpA	SNP	0.01	0.12	1.18	0.2	0.01	0.17	1.01	0.23	0.01	0.07	1.25	0.73
		WT	1.13	3.31	6.47		0.01	0.17	1.01		0.47	1.42	5.12	
		HT	0.46	2.01	4.62		0.46	2.14	4.62		0.19	1.71	6.51	
	Ppg	SNP	0.29	1.66	4.85	0.40	0.15	2.24	6.81	0.29	0.43	0.84	3.82	0.93
		WT	1.19	3.01	12.09		1.22	4.67	12.30		1.19	2.51	9.24	
		HT	0.87	2.98	8.31		1.35	2.98	8.84		0.74	3.09	7.88	
	D	SNP	0.69	2.39	7.29	0.48	0.61	2.02	7.15	0.36	0.74	3.21	7.74	0.87
		WT	0.72	3.06	8.98		0.72	3.21	8.98		0.47	2.78	11.22	
		HT	0.60	2.36	5.94		0.51	2.84	5.28		1.02	2.30	6.93	
	D+LpA	SNP	0.23	2.24	7.31	0.86	0.01	1.97	6.12	1.00	0.32	2.41	7.64	0.60
		WT	0.46	2.24	7.06		0.72	3.00	8.51		0.46	1.48	5.32	
		HT	0.50	3.73	6.51		0.98	3.73	6.31		0.26	3.55	10.36	
		SNP	0.65	3.26	6.93		0.54	2.06	6.73		2.82	4.39	7.93	
rs1800893 Block 3	U	WT	0.01	0.40	0.65	0.43	0.01	0.47	0.65	0.21	0.01	0.01	0.54	0.80
		HT	0.01	0.21	0.60		0.01	0.10	0.54		0.01	0.23	0.60	
		SNP	0.01	0.47	0.65		0.15	0.35	0.69		0.01	0.47	0.60	
	PHA	WT	0.01	0.23	0.93	0.99	0.01	0.33	0.93	1.00	0.01	0.20	0.96	0.96
		HT	0.01	0.24	0.81		0.01	0.23	0.81		0.01	0.47	0.81	
		SNP	0.01	0.20	1.26		0.01	0.23	1.18		0.01	0.12	1.27	
	LpA	WT	0.56	3.01	6.49	0.21	0.86	3.54	6.48	0.45	0.47	1.56	6.51	0.73
		HT	0.56	2.61	5.19		0.80	2.78	5.19		0.19	1.71	10.18	
		SNP	0.15	1.31	3.82		0.06	1.54	5.42		0.45	1.24	3.34	
	Ppg	WT	0.84	3.02	11.95	0.33	0.81	3.76	12.02	0.17	1.19	3.02	9.24	0.89
		HT	0.98	3.69	10.72		1.54	3.69	10.72		0.74	3.09	8.31	
		SNP	0.63	2.29	6.76		0.54	1.55	4.76		0.81	3.26	7.25	
	D	WT	0.56	2.78	8.98	0.25	0.56	2.79	7.70	0.13	1.12	2.78	11.22	0.84
		HT	0.98	3.36	7.93		0.98	3.57	7.54		1.02	2.48	8.47	
		SNP	0.01	1.97	6.12		0.01	0.99	3.09		0.32	2.57	7.64	

D+LpA	WT	0.34	1.97	7.00		0.22	2.32	6.93		0.46	1.27	7.06	
	HT	1.56	4.00	8.56	0.47	1.62	3.87	6.67	0.50	0.50	5.53	12.15	0.54
	SNP	0.60	3.02	7.43		0.49	1.48	6.93		2.82	4.40	7.93	
rs3024496													
Block 3 U	WT	0.01	0.47	0.66		0.01	0.47	0.65		0.01	0.40	0.74	
	HT	0.01	0.10	0.56	0.33	0.01	0.06	0.54	0.25	0.01	0.19	0.60	0.90
	SNP	0.01	0.22	0.65		0.12	0.22	0.67		0.01	0.17	0.63	
PHA	WT	0.01	0.33	0.98		0.01	0.33	1.17		0.01	0.23	0.80	
	HT	0.01	0.23	0.83	0.87	0.01	0.24	0.81	0.87	0.01	0.09	1.04	0.98
	SNP	0.01	0.18	1.18		0.01	0.23	1.18		0.01	0.12	1.25	
LpA	WT	1.13	3.03	6.49		1.13	3.86	6.49		0.48	1.71	5.12	
	HT	0.46	2.14	4.69	0.08	0.65	2.34	4.76	0.16	0.01	1.26	4.17	0.67
	SNP	0.06	0.98	3.82		0.01	0.98	5.64		0.45	1.24	3.13	
Ppg	WT	1.12	3.01	12.09		0.80	3.76	12.09		1.19	3.01	9.24	
	HT	0.96	2.90	8.31	0.35	1.44	3.07	9.78	0.17	0.60	0.97	7.88	0.49
	SNP	0.61	2.34	6.76		0.12	1.44	5.77		0.81	3.26	7.25	
D	WT	0.72	2.90	8.47		0.64	3.06	8.46		1.12	2.78	8.47	
	HT	0.84	2.51	5.94	0.35	0.55	3.34	5.72	0.16	0.93	1.65	5.94	0.93
	SNP	0.01	1.55	7.12		0.01	0.84	2.97		0.32	2.57	7.64	
D+LpA	WT	0.46	2.24	6.93		0.72	3.00	6.93		0.46	1.48	5.32	
	HT	0.50	3.73	6.60	0.90	0.98	3.73	6.51	0.69	0.01	1.04	8.56	0.40
	SNP	0.54	3.21	6.93		0.01	1.27	6.93		2.82	4.40	7.93	
rs3024498													
Block 4 U	WT	0.01	0.32	0.61		0.01	0.34	0.61		0.01	0.17	0.66	
	HT	0.01	0.17	0.50	0.11	0.01	0.15	0.47	0.11	0.01	0.21	0.58	0.70
	SNP	0.01	0.65	0.84		0.07	0.71	1.13		0.01	0.49	0.65	
PHA	WT	0.01	0.33	0.98		0.01	0.27	0.84		0.01	0.40	1.08	
	HT	0.01	0.01	0.81	0.43	0.01	0.01	0.81	0.22	0.01	0.18	0.93	0.22
	SNP	0.01	0.18	0.84		0.12	0.84	1.41		0.01	0.02	0.12	
LpA	WT	0.49	2.58	5.46		0.67	3.57	6.07		0.47	1.71	4.19	
	HT	0.46	1.89	4.52	0.43	0.31	2.37	3.77	0.29	0.52	1.47	10.28	0.42
	SNP	0.43	1.31	2.44		0.52	2.10	10.09		0.43	0.75	1.64	
Ppg	WT	0.98	2.97	9.41		1.13	2.97	11.41		0.90	2.76	8.71	
	HT	0.74	3.00	10.76	0.53	0.98	2.91	8.25	0.52	0.74	6.48	11.79	0.79
	SNP	0.54	2.20	4.03		0.28	1.40	7.95		1.02	2.83	3.87	
D	WT	0.58	2.73	7.53		0.56	2.90	7.52		0.60	2.30	8.47	
	HT	0.57	2.78	7.48	0.43	0.12	2.86	6.08	0.63	1.02	2.74	9.36	0.35
	SNP	0.01	1.13	4.73		0.12	1.13	5.43		0.01	1.61	4.61	
D+LpA	WT	0.46	2.28	7.00		0.47	2.66	6.81		0.46	1.97	7.66	
	HT	0.98	4.00	7.93	0.54	0.49	3.73	6.73	0.83	1.57	6.16	13.46	0.55
	SNP	0.65	2.05	3.31		0.54	1.27	6.93		0.65	2.82	3.21	

1.Q, first quartile; Med, median; 3.Q, third quartile; p(KW), p-value from Kruskal-Wallis test. CBMCs all, CBMCs of all mothers, not stratified for maternal atopy. Bold p-values, p≤0.10.

Table E5: Prevalence of AD and wheeze in the first 3 years of life (Total N=200).

Outcome (3ys)	N	%
neither AD nor wheeze	92	46.0
AD	59	29.5
only AD	33	16.5
wheeze	75	37.5
one episode	66	33.0
recurrent episodes	9	4.5
only wheeze	49	24.5
one episode	42	21.0
recurrent episodes	7	3.5
AD and wheeze	26	13.0
one episode	24	12.0
recurrent episodes	2	1.0

Wheeze, any wheezy symptoms in the first 3 years of life; AD, any symptoms of atopic dermatitis in the first 3 years of life; AD/wheeze, symptoms of AD and/or wheeze in the first 3 years of life. %, percentage of children with respective outcome at the age of 3 years.

Table E6. Effect of *IL-10* SNPs on different clinical outcomes

SNP/ LD-Block	outcome		OR	95%-CI	p
rs79309463	wheeze	WT	1.00	–	–
		HT vs. WT	0.68	0.32-1.42	0.30
		SNP vs. WT	3.50	0.86-14.30	0.08
	AD/wheeze	WT	1.00	–	–
		HT vs. WT	0.67	0.33-1.37	0.28
		SNP vs. WT	7.29	0.89-59.64	0.06
rs10494879	AD/wheeze	WT	1.00	–	–
		HT vs. WT	0.89	0.45-1.75	0.73
		SNP vs. WT	3.01	0.99-9.12	0.05
rs1800890 (Block 1)	AD/wheeze	WT	1.0	–	–
		HT vs. WT	0.86	0.40-1.87	0.7034
		SNP vs. WT	2.30	0.85-6.20	0.10
	AD	WT	1.00	–	–
		HT vs. WT	0.87	0.44-1.72	0.68
		SNP vs. WT	2.87	0.95-8.65	0.06
rs1878672 (Block 3)	AD/wheeze	WT	1.00	–	–
		HT vs. WT	1.36	0.66-2.80	0.40
		SNP vs. WT	2.60	1.09-6.18	0.03
rs1800893 (Block 3)	AD/wheeze	WT	1.00	–	–
		HT vs. WT	1.35	0.66-2.79	0.41
		SNP vs. WT	2.90	1.17-7.19	0.022
rs3024498 (Block 4)	wheeze	WT	1.00	–	–
		HT vs. WT	0.72	0.34-1.52	0.39
		SNP vs. WT	3.97	1.17-13.55	0.03
	AD/wheeze	WT	1.00	–	–
		HT vs. WT	0.66	0.32-1.33	0.24
		SNP vs. WT	4.90	1.04-23.06	0.04

Wheeze, any wheezy in the first 3 years of life; AD, any symptoms of AD in the first 3 years of life. AD/wheeze, symptoms of AD and/or wheeze in the first 3 years of life. OR, odds ratio; CI, confidence interval; WT, wildtype; HT, heterozygous carriers of the SNP; SNP, homozygous carriers of the SNP. p, p-value from Chi2-test.

Table E7: Association of immunology and outcome at age 3 years stratified for CBMCs of non-atopic/atopic mothers (overview).

Outcome (3ys)	Variable	Stimulation condition		
		CBMCs all	CBMCs of non-atopic mothers	CBMCs of atopic mothers
Wheeze	IL-5	↑ U*	↑ U*	
	TNF- α		↑ U*	
	FOXP3 (dct)	↑ PHA*		
	LAG3 (dct)	↑ PHA* Ppg*	↑ PHA* LpA Ppg	
AD	IL-5	↓ PHA LpA* Ppg D+LpA		
	IL-10 (dct)	↓ U LpA* Ppg*		
	TNF- α	↓ LpA		
	GM-CSF	↓ LpA*		↓ LpA
	FOXP3 (dct)		↓ D	↓ PHA* (fd)
	LAG3 (dct)	↓ PHA*		↓ PHA*
AD and/or wheeze	IL-5	↑ U* ↓ LpA*	↑ U*	↓ LpA
	TNF- α	↑ U* ↓ LpA*	↑ U* ↓ LpA	↓ LpA*
	LAG3 (dct)	↑ LpA Ppg*	↑ PHA LpA	

↑: secretion/expression upregulated in carriers with the respective outcome.

↓: secretion/expression downregulated in carriers with the respective outcome. IL-5, TNF- α and GM-CSF were measured at protein level; FOXP3, LAG3 and IL-10 at mRNA level.

CBMCs all, CBMCs of all mothers, not stratified for maternal atopy. U, unstimulated; PHA, phytohemagglutinin; LpA, Lipid A; Ppg, peptidoglycan; D, *Dermatophagoides pteronyssinus*; (dct), delta CT; (fd), gene expression as fold difference. p-value from Wilcoxon test.

* $p \leq 0.05$, all other presented results are $p \leq 0.1$. Wheeze, any wheezy symptoms in the first 3 years of life; AD, any symptoms of atopic dermatitis in the first 3 years of life; AD/wheeze, symptoms of AD and/or wheeze in the first 3 years of life. Total N=200; number of subjects were variable depending on available measurements.

Table E8. Immunology of carriers of SNP diplotype 2 and 3 compared to SNP diplotype 0

Immunology	diplotype 2 (SNP 2-5)	diplotype 3 (SNP 1-6)
IL-5	↓ D*	↓ LpA* D
IFN-γ	↓ LpA D*	n.d.
TNF-α	n.d.	↓ LpA* Ppg* D* D+LpA*
GM-CSF	↑ U*	↓ PHA* LpA* Ppg D* D+LpA*

SNP 1: Distal promoter SNP rs79309463 (deletion); SNP 2: Distal promoter SNP rs10494879; SNP 3: rs1800890 (Block 1); SNP 4: rs1878672 (Block 3); SNP 5: rs1800893 (Block 3); SNP 6: rs3024498 (Block 4).

↑: secretion [pg/ml] upregulated compared to diplotype 0 (none of the 6 SNPs); ↓: secretion [pg/ml] downregulated compared to diplotype 0 (none of the 6 SNPs). U, unstimulated; PHA, phytohemagglutinin; LpA, Lipid A; Ppg, peptidoglycan; D, *Dermatophagoides pteronyssinus*. p-value from Wilcoxon test. * $p \leq 0.05$, all other presented results are $p \leq 0.1$.

Online Repository

Interleukin-10 polymorphisms influence neonatal immune responses, atopic dermatitis and wheeze with 3 years

Diana Raedler ^a, Sabina Illi, PhD ^a, Leonardo Araujo Pinto, MD ^b, Erika von Mutius, MD ^a, Thomas Illig, PhD ^{c, d}, Michael Kabesch, MD ^e, Bianca Schaub, MD ^a

^aUniversity Children's Hospital Munich, Department of Pulmonary & Allergy, LMU Munich, Germany; ^bInstituto de Pesquisas Biomédicas, Pontificia Universidade Católica do Rio Grande do Sul; ^cInstitute of Epidemiology, Helmholtz Centre Munich, German Research Centre for Environmental Health, Neuherberg, Germany; ^dHannover Unified Biobank, Hannover Medical School, Hannover, Germany; ^eClinic for Paediatric Pneumology, Allergology and Neonatology, Hannover Medical School, Hannover, Germany

Corresponding author

Bianca Schaub, MD
University Children's Hospital Munich
Lindwurmstr. 4
80337 Munich, Germany
Ph: +49-89-5160-7856
Fax: +49-89-5160-4764
Email: Bianca.Schaub@med.uni-muenchen.de

METHODS

Study population

Inclusion criteria comprised healthy neonates and mothers with uncomplicated pregnancy.

Exclusion criteria included preterm deliveries, multiple gestation, perinatal infections comprising fever around birth, maternal use of antibiotics in the last trimester and maternal chronic diseases.^{E1}

Potential confounders, including maternal atopy, smoking, sex, birth characteristics, race/ethnicity, siblings, education, previous caesarean section, miscarriage and birth characteristics, were determined by questionnaires.

Real-time quantitative RT-PCR

Total RNA was isolated from CBMCs with TRI reagent, cDNA synthesis was performed using reverse transcriptase (Invitrogen, Karlsruhe, Germany). Specific primer pairs (18S, FOXP3, GITR, LAG3, IL-10) were designed with Vector NTI advance10 (Invitrogen, Karlsruhe, Germany).^{E2} *IL-10* mRNA levels were measured in a subgroup of children (n=51), where RNA was available from unstimulated, LpA-, Ppg- and D-stimulated PBMCs. Gene-specific PCR-products were measured continuously by means of iCycler Real-Time PCR-Detection-System (Bio-Rad) for 40 cycles. Direct detection of the PCR product was monitored by measuring the increase in fluorescence caused by the binding of SYBR Green to dsDNA as described.^{E2} The threshold cycle (ct) of each target product was determined and set in relation to the amplification plot of 18S (Δ ct), whereas a higher Δ ct refers to a lower gene expression. The difference in Δ ct was used to calculate the fold difference (fd). Relative quantitative (fold difference) results were used to determine changes in gene expression in stimulated as compared to unstimulated samples.^{E3} mRNA expression of each gene is described as gene expression.

Figure E1

Linkage disequilibrium (R^2 plots) for the eight investigated *IL-10* polymorphisms within our study population. Shades in LD plot (Haploview): white ($R^2=0$), gray ($0<R^2<1$), black ($R^2=1$).

References

- E1. Liu J, Raedler D, Illi S, Klucker E, Turan E, von Mutius E, et al. TLR2 polymorphisms influence neonatal regulatory T cells depending on maternal atopy. *Allergy* 2011;66:1020-9.
- E2. Schaub B, Liu J, Hoppler S, Haug S, Sattler C, Lluís A, et al. Impairment of T-regulatory cells in cord blood of atopic mothers. *J Allergy Clin Immunol* 2008;121:1491-9, 9 e1-13.
- E3. Heid CA, Stevens J, Livak KJ and Williams PM. Real time quantitative PCR. *Genome Res* 1996;6:986-94.

