Supplementary information

Title: Meta-analysis of genome-wide association studies identifies 10 loci influencing allergic sensitization

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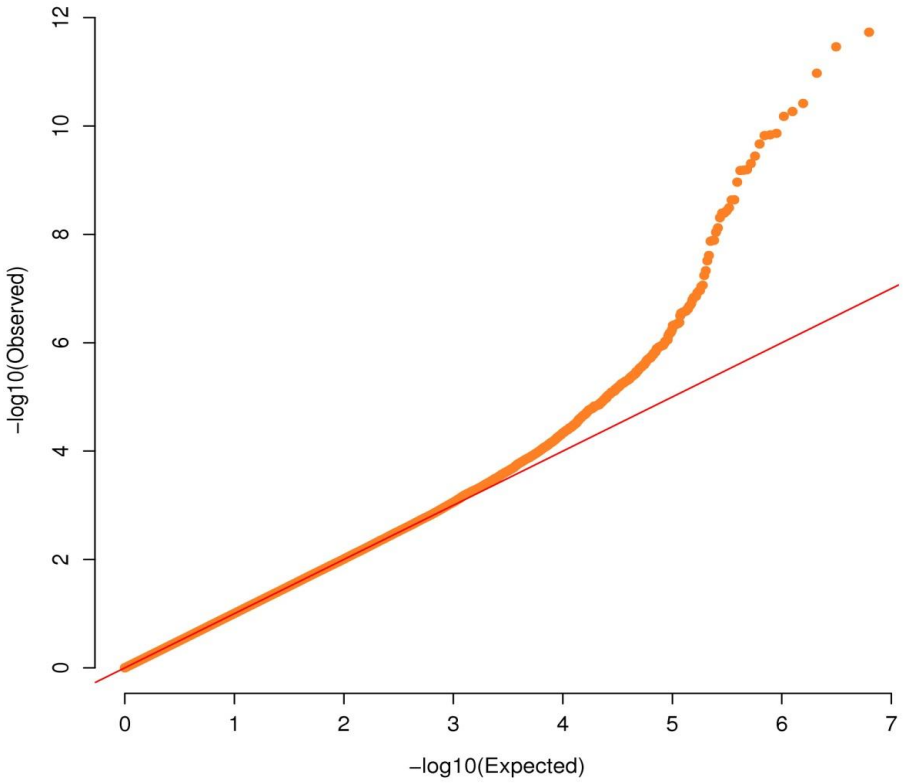
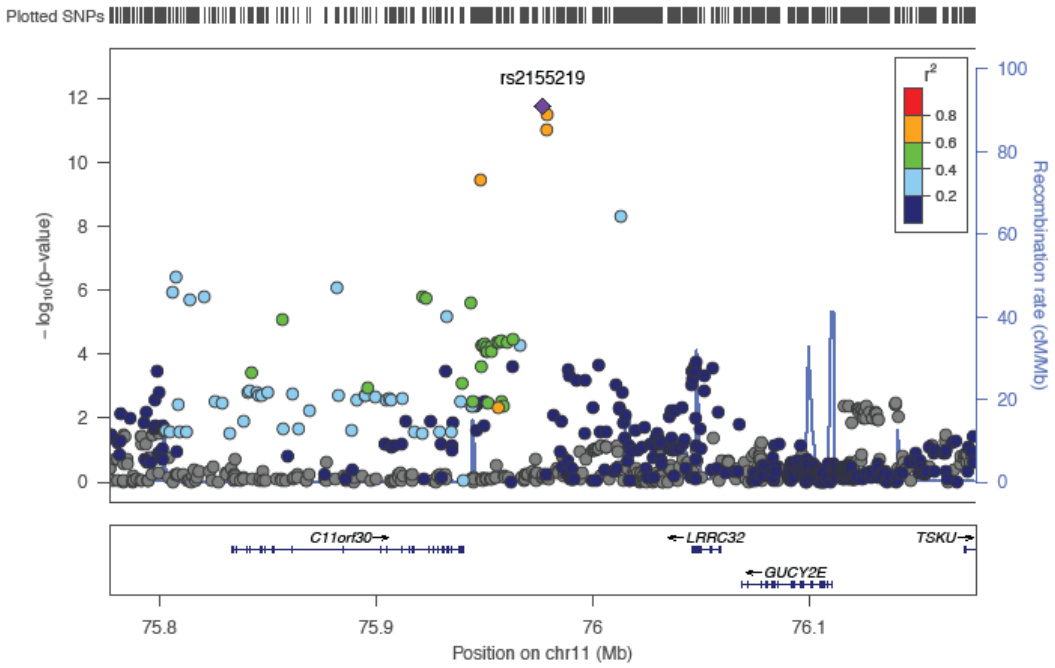
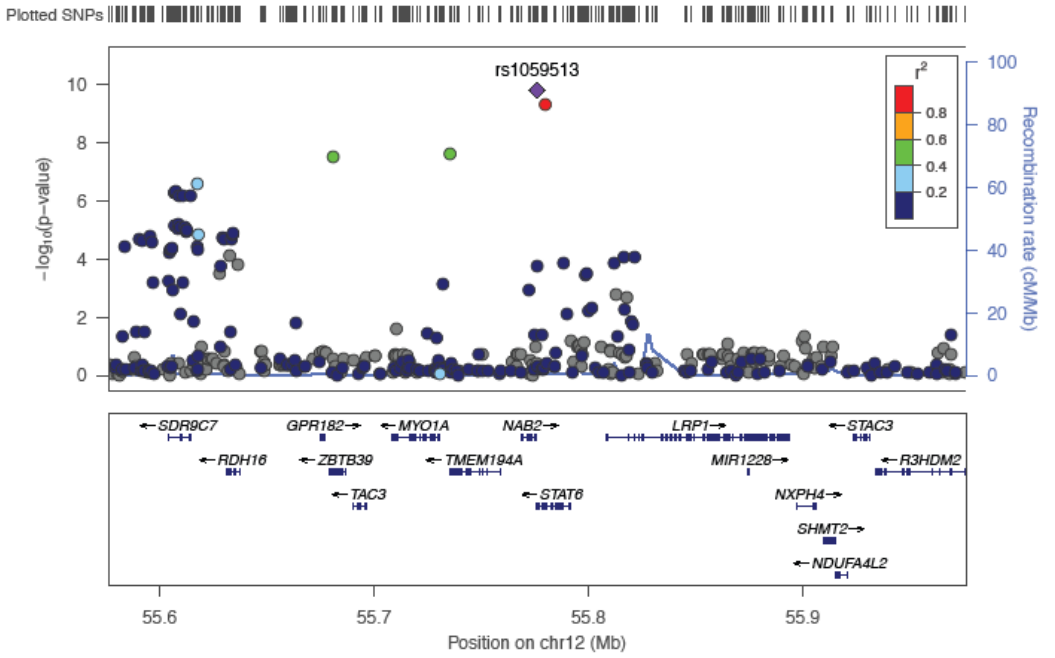
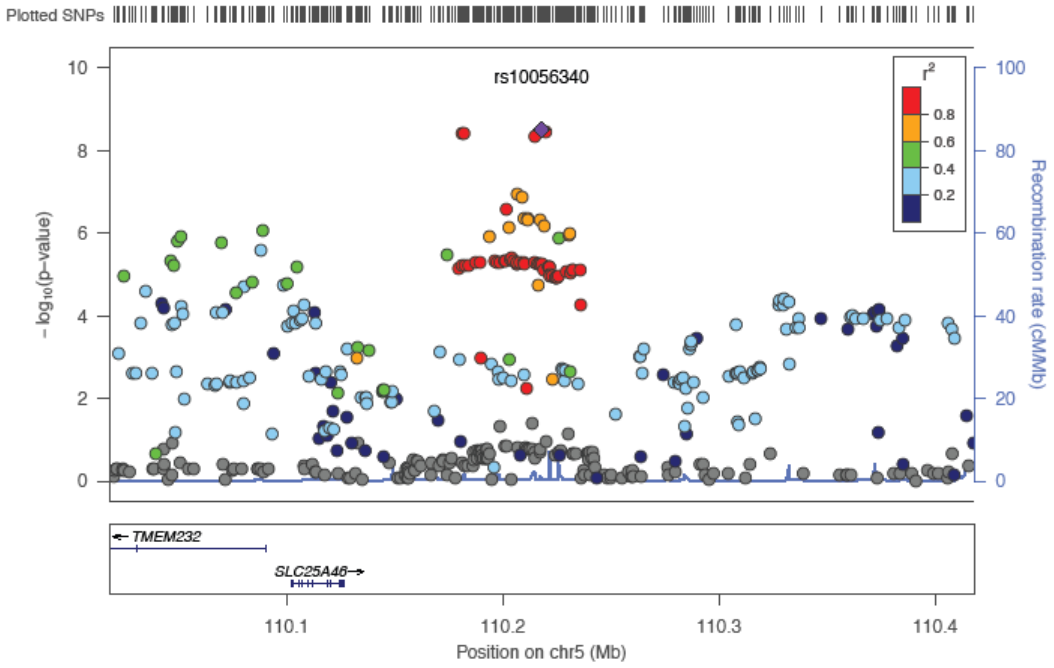
Supplementary figure 1. QQ-plot for the discovery genome-wide association meta-analysis



Supplementary Figure 2. Regional association plots for the 10 genome-wide significant loci






Plotted SNPs
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r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
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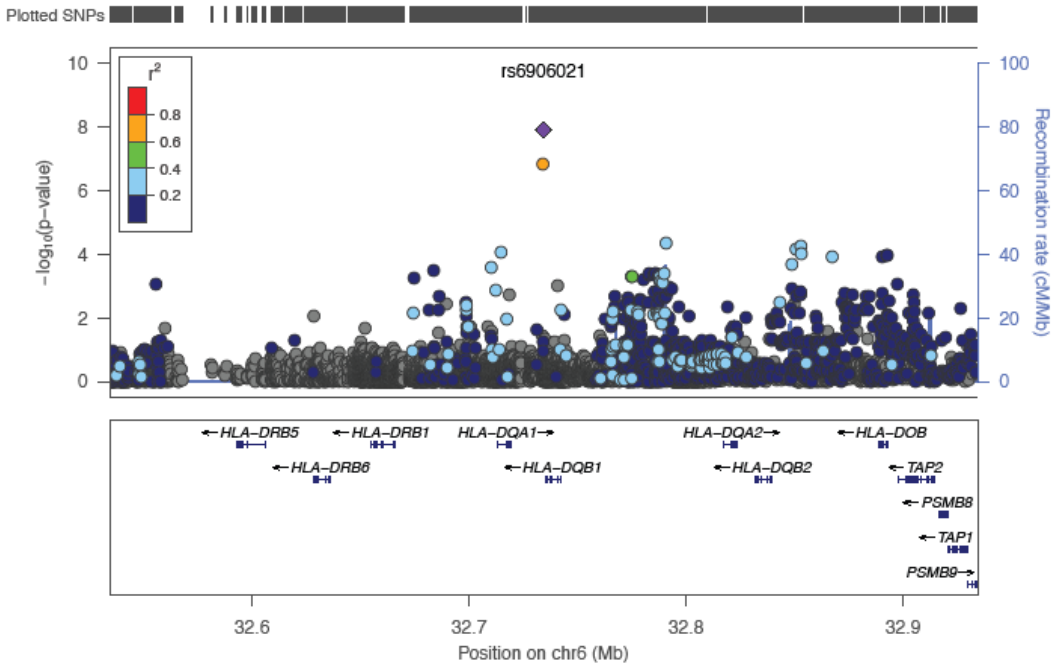
SLC25A46
110.1
110.2
110.3
110.4
Position on chr5 (Mb)


Plotted SNPs
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r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
HLA−DRB5
HLA−DRB1
HLA−DQA1
HLA−DQA2
HLA−DOB
HLA−DRB6
HLA−DQB1
HLA−DQB2
TAP2
PSMB8
TAP1
PSMB9
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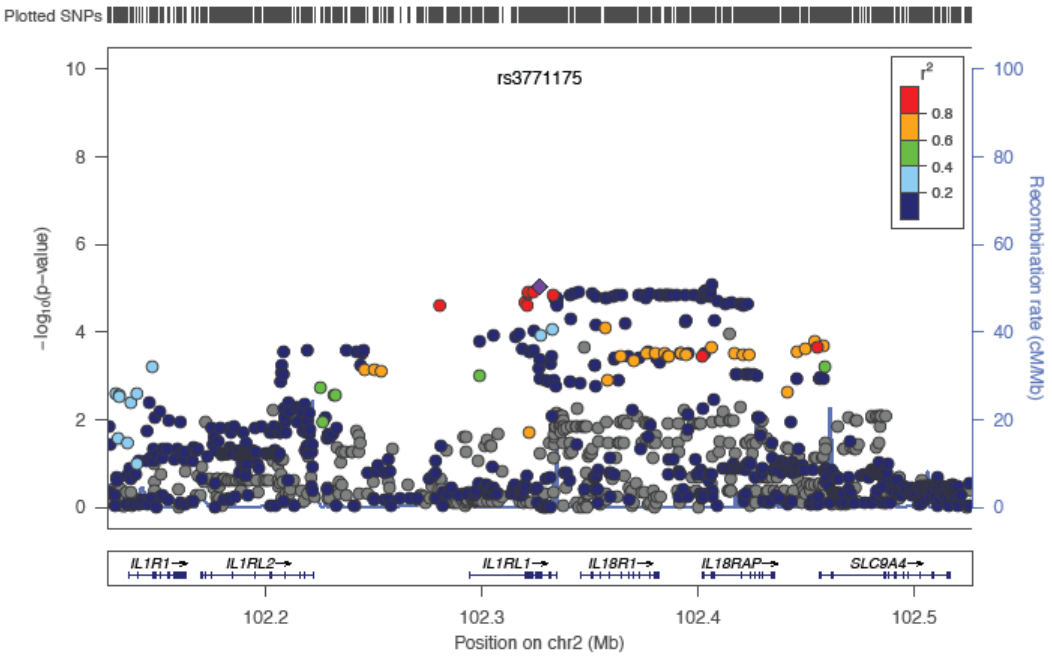
32.7
32.8
32.9
Position on chr6 (Mb)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r²
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0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
IL1R1
IL1RL2
IL1RL1
IL18R1
IL18RAP
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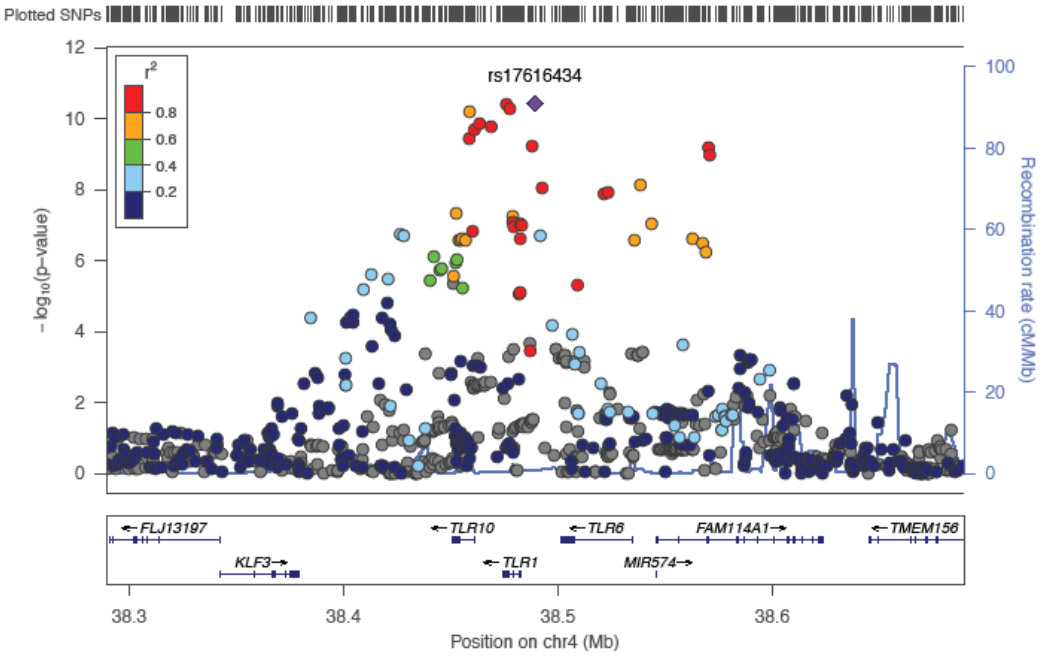
102.2
102.3
102.4
102.5
Position on chr2 (Mb)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r²
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0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
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TLR10
TLR6
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TMEM156
KLF3
TLR1
MIR574
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38.4
38.5
38.6
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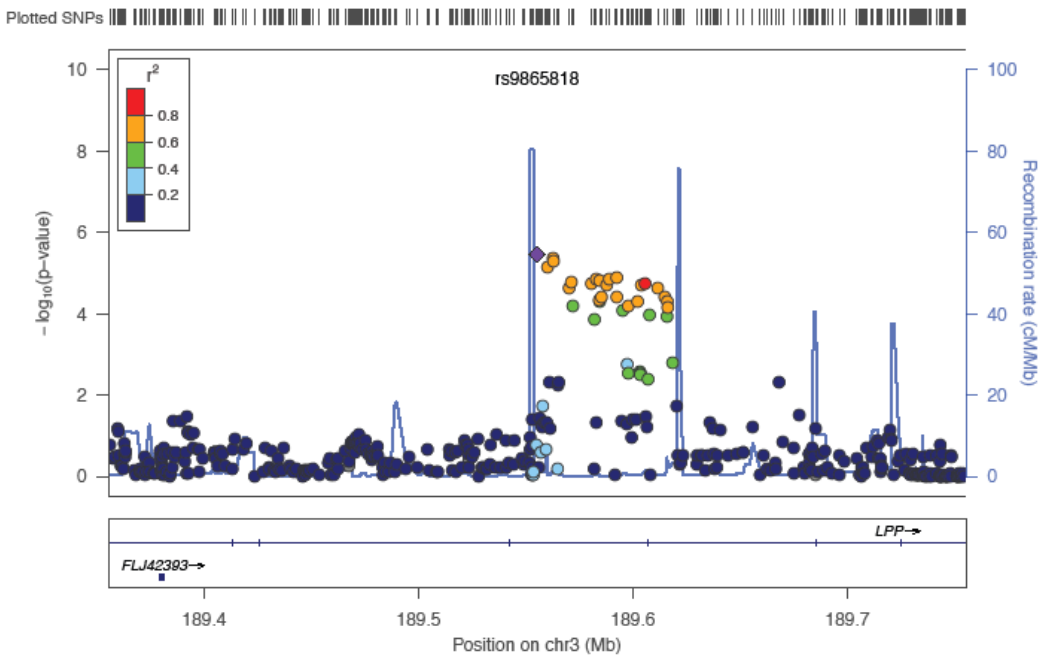
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r²
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0.6
0.4
0.2
10
8
6
4
2
0
100
80
60
40
20
0
− log10(p−value)
Recombination rate (cM/Mb)
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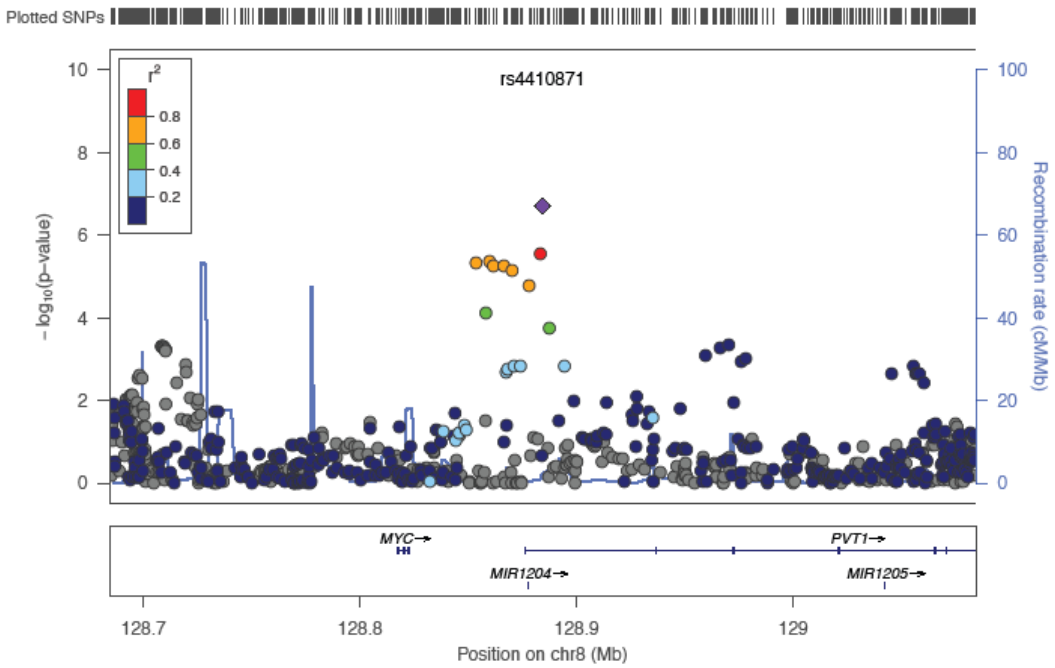
FLJ42393
189.4
189.5
189.6
189.7
Position on chr3 (Mb)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0.4
0.2
10
8
6
4
2
0
100
80
60
40
20
0
− log10(p−value)
Recombination rate (cM/Mb)
MYC
PVT1
MIR1204
MIR1205
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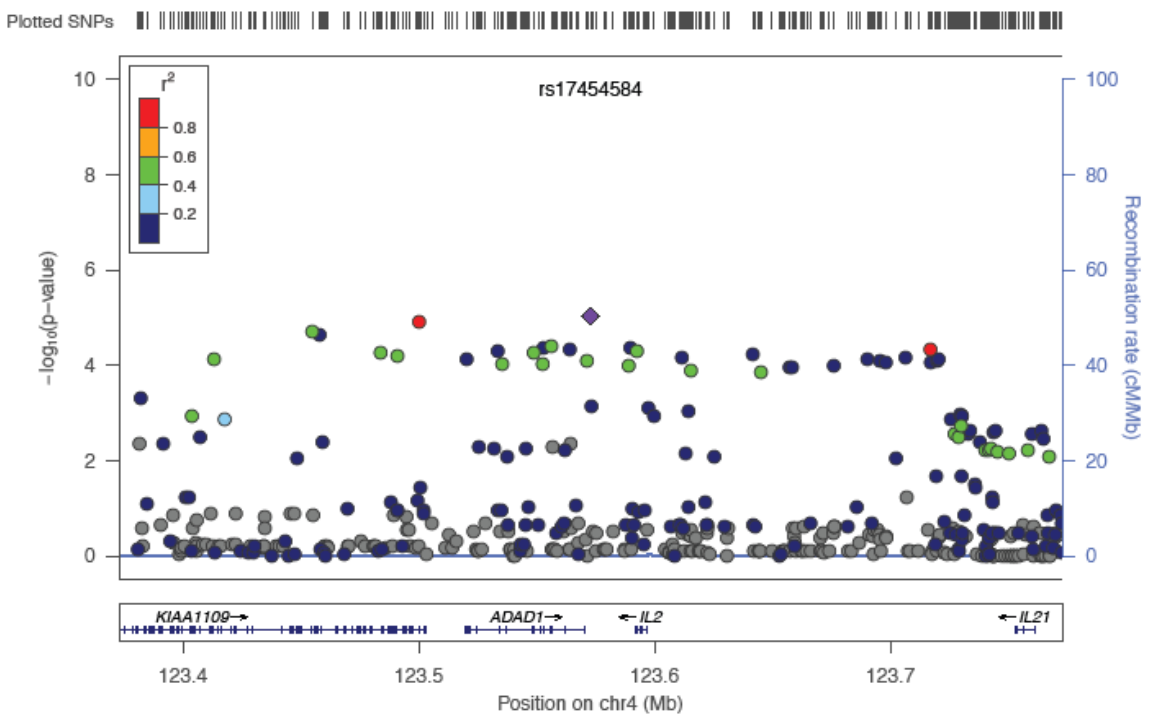
128.8
128.9
129
Position on chr8 (Mb)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rs17454584
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
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ADAD1→
←IL2
←IL21
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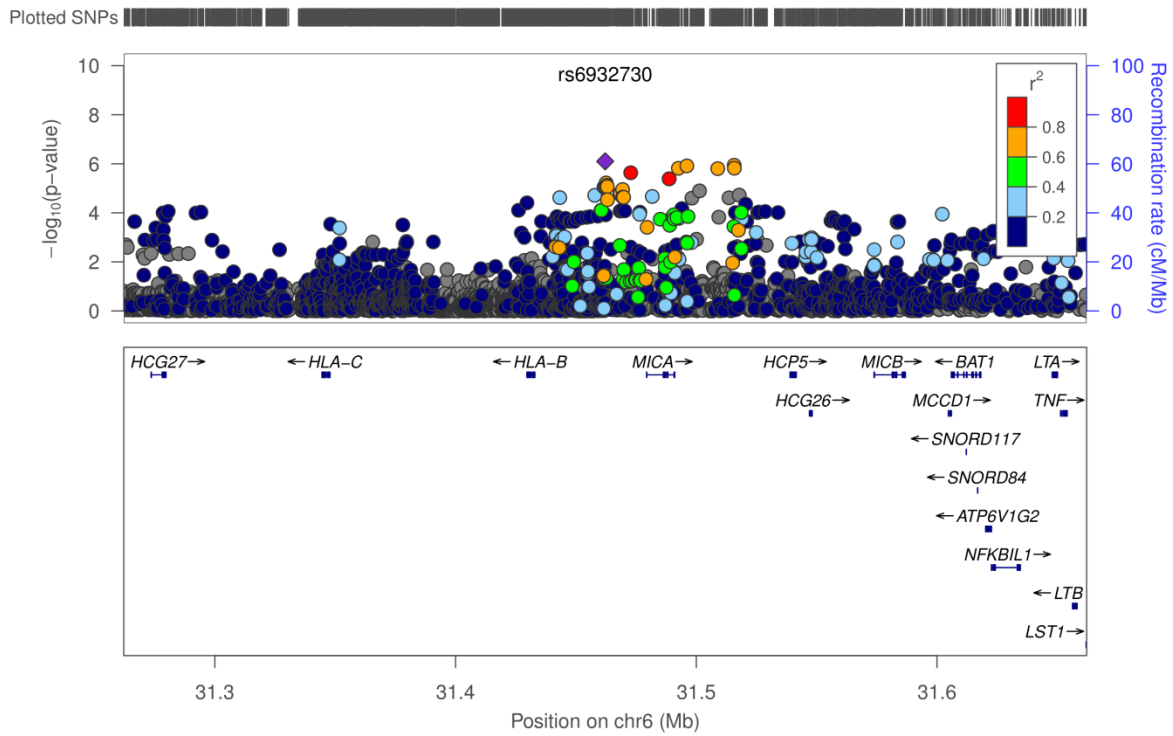
123.5
123.6
123.7
Position on chr4 (Mb)


Plotted SNPs
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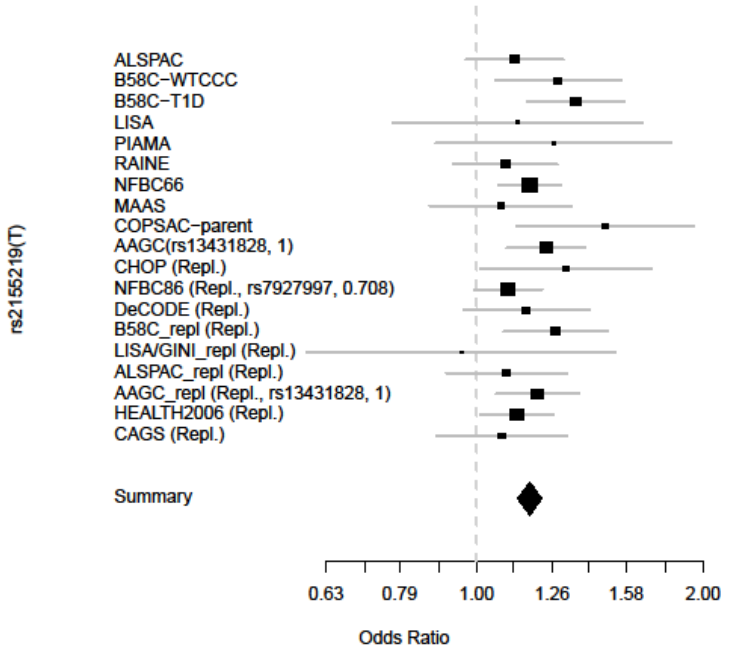
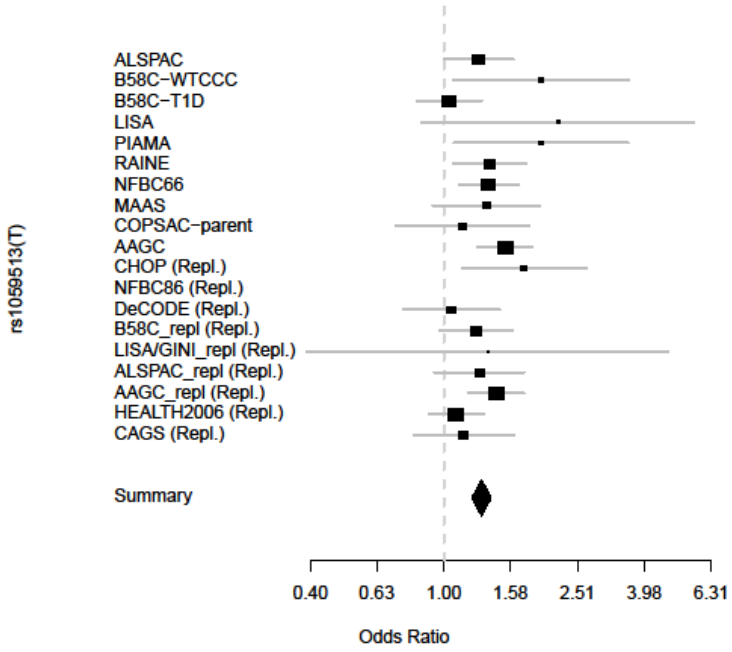
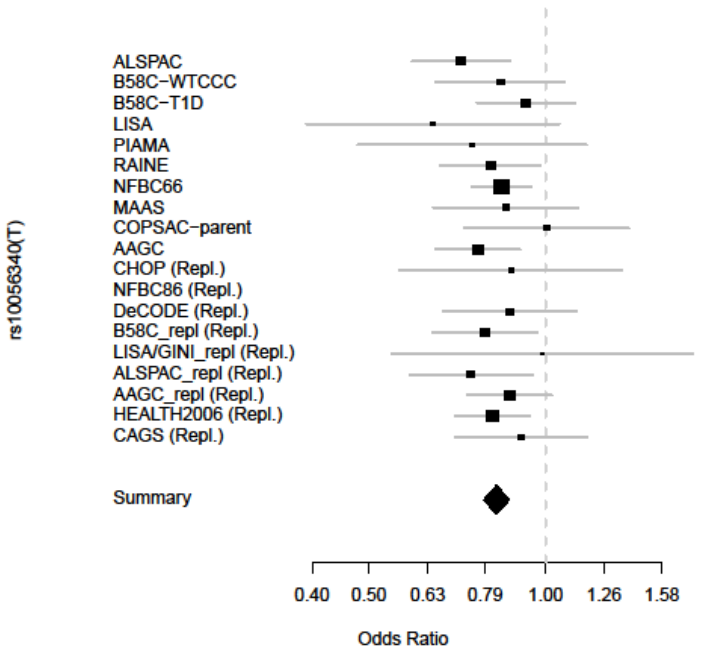
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
HCG27→
←HLA−C
←HLA−B
MICA→
HCP5→
MICB→
←BAT1
LTA→
HCG26→
MCCD1→
TNF→
←SNORD117
←SNORD84
←ATP6V1G2
NFKBIL1→
←LTB
LST1→
31.3
31.4
31.5
31.6
Position on chr6 (Mb)

Supplementary Figure 3. Forest plots of the association with sensitization for the 10 genome-wide significant SNPs for discovery and replication studies. The effect allele is shown in brackets after the SNP name. For some SNPs a proxy was used in the replication studies, this is indicated by proxy SNP rs-number and r^2-value after the cohort name.



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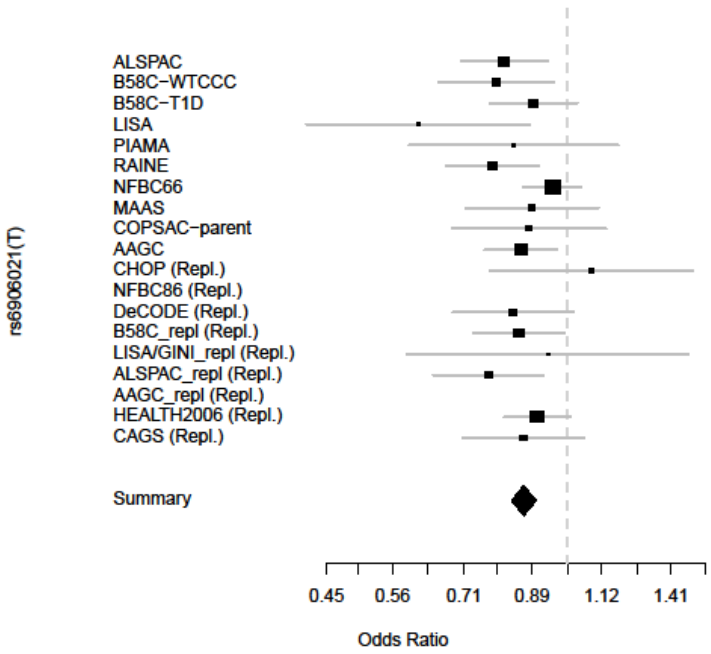
ALSPAC
B58C−WTCCC
B58C−T1D
LISA
PIAMA
RAINE
NFBC66
MAAS
COPSAC−parent
AAGC
CHOP (Repl.)
NFBC86 (Repl.)
DeCODE (Repl.)
B58C_repl (Repl.)
LISA/GINI_repl (Repl.)
ALSPAC_repl (Repl.)
AAGC_repl (Repl.)
HEALTH2006 (Repl.)
CAGS (Repl.)
Summary
0.40 0.50 0.63 0.79 1.00 1.26 1.58
Odds Ratio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ALSPAC
B58C−WTCCC
B58C−T1D
LISA
PIAMA
RAINE
NFBC66
MAAS
COPSAC−parent
AAGC
CHOP (Repl.)
NFBC86 (Repl.)
DeCODE (Repl.)
B58C_repl (Repl.)
LISA/GINI_repl (Repl.)
ALSPAC_repl (Repl.)
AAGC_repl (Repl.)
HEALTH2006 (Repl.)
CAGS (Repl.)
Summary
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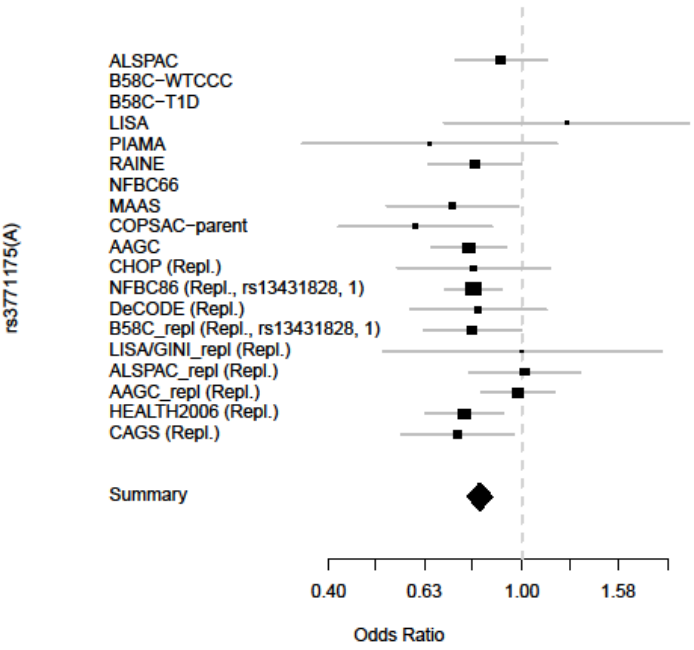
Odds Ratio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ALSPAC
B58C−WTCCC
B58C−T1D
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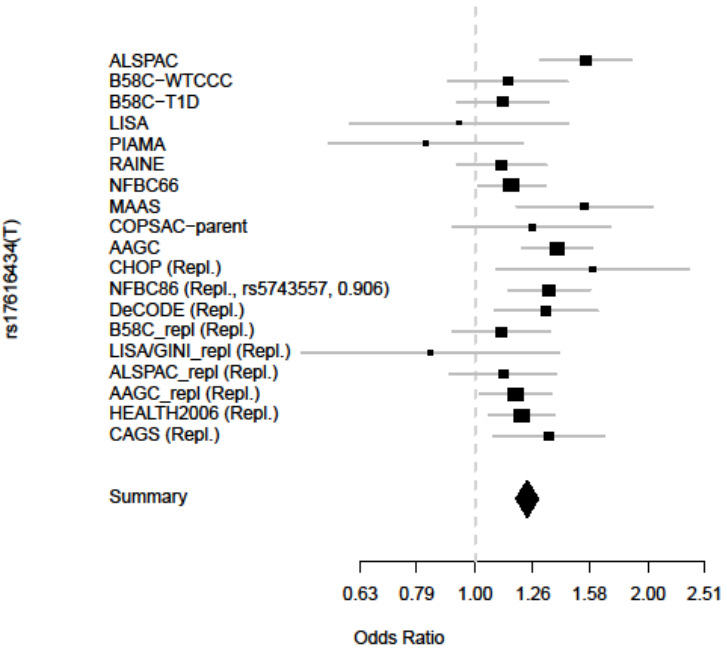
PIAMA
RAINE
NFBC66
MAAS
COPSAC−parent
AAGC
CHOP (Repl.)
NFBC86 (Repl., rs13431828, 1)
DeCODE (Repl.)
B58C_repl (Repl., rs13431828, 1)
LISA/GINI_repl (Repl.)
ALSPAC_repl (Repl.)
AAGC_repl (Repl.)
HEALTH2006 (Repl.)
CAGS (Repl.)
Summary
0.40
0.63
1.00
1.58
Odds Ratio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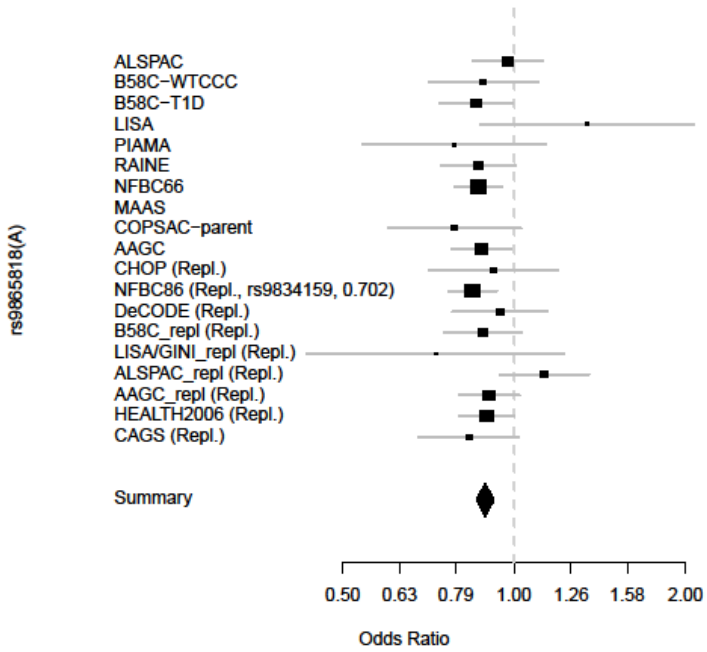
ALSPAC
B58C−WTCCC
B58C−T1D
LISA
PIAMA
RAINE
NFBC66
MAAS
COPSAC−parent
AAGC
CHOP (Repl.)
NFBC86 (Repl., rs5743557, 0.906)
DeCODE (Repl.)
B58C_repl (Repl.)
LISA/GINI_repl (Repl.)
ALSPAC_repl (Repl.)
AAGC_repl (Repl.)
HEALTH2006 (Repl.)
CAGS (Repl.)
Summary
0.63
0.79
1.00
1.26
1.58
2.00
2.51
Odds Ratio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B58C−WTCCC
B58C−T1D
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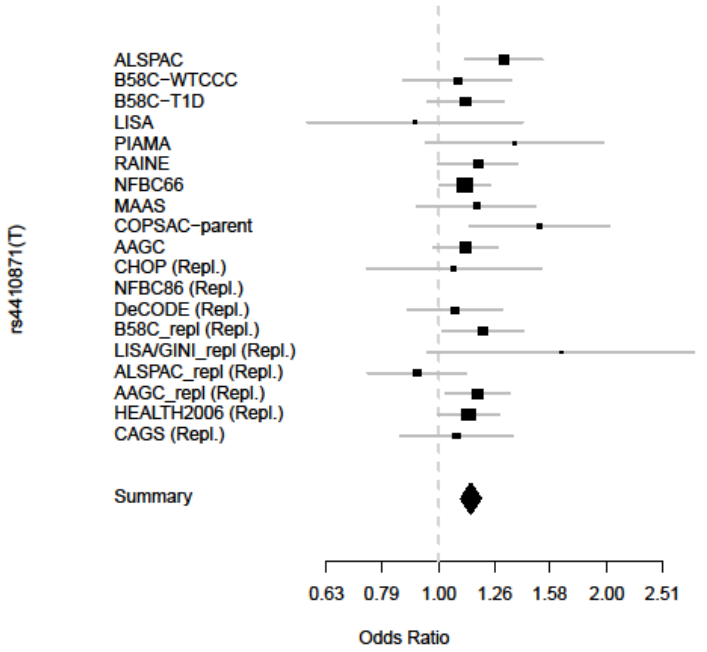
PIAMA
RAINE
NFBC66
MAAS
COPSAC−parent
AAGC
CHOP (Repl.)
NFBC86 (Repl., rs9834159, 0.702)
DeCODE (Repl.)
B58C_repl (Repl.)
LISA/GINI_repl (Repl.)
ALSPAC_repl (Repl.)
AAGC_repl (Repl.)
HEALTH2006 (Repl.)
CAGS (Repl.)
Summary
0.50 0.63 0.79 1.00 1.26 1.58 2.00
Odds Ratio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B58C−T1D
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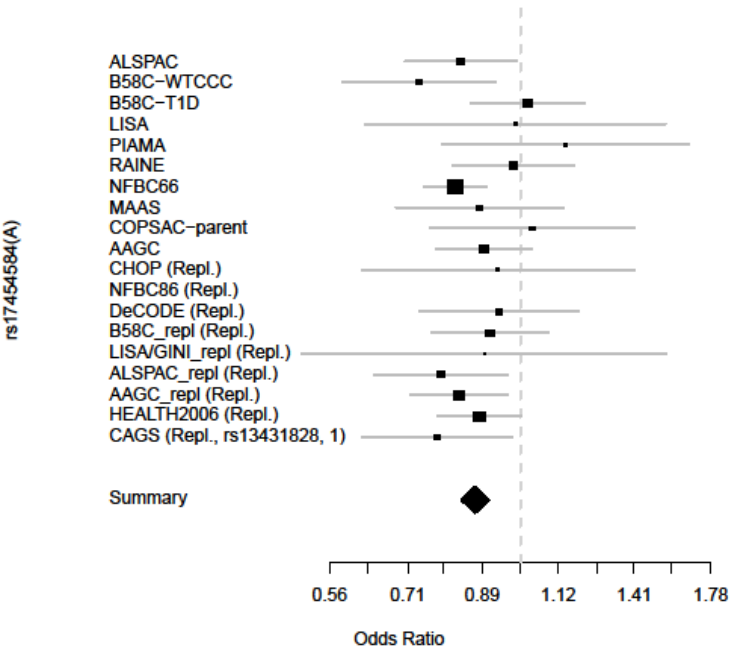
PIAMA
RAINE
NFBC66
MAAS
COPSAC−parent
AAGC
CHOP (Repl.)
NFBC86 (Repl.)
DeCODE (Repl.)
B58C_repl (Repl.)
LISA/GINI_repl (Repl.)
ALSPAC_repl (Repl.)
AAGC_repl (Repl.)
HEALTH2006 (Repl.)
CAGS (Repl.)
Summary
0.63 0.79 1.00 1.26 1.58 2.00 2.51
Odds Ratio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ALSPAC
B58C−WTCCC
B58C−T1D
LISA
PIAMA
RAINE
NFBC66
MAAS
COPSAC−parent
AAGC
CHOP (Repl.)
NFBC86 (Repl.)
DeCODE (Repl.)
B58C_repl (Repl.)
LISA/GINI_repl (Repl.)
ALSPAC_repl (Repl.)
AAGC_repl (Repl.)
HEALTH2006 (Repl.)
CAGS (Repl., rs13431828, 1)
Summary
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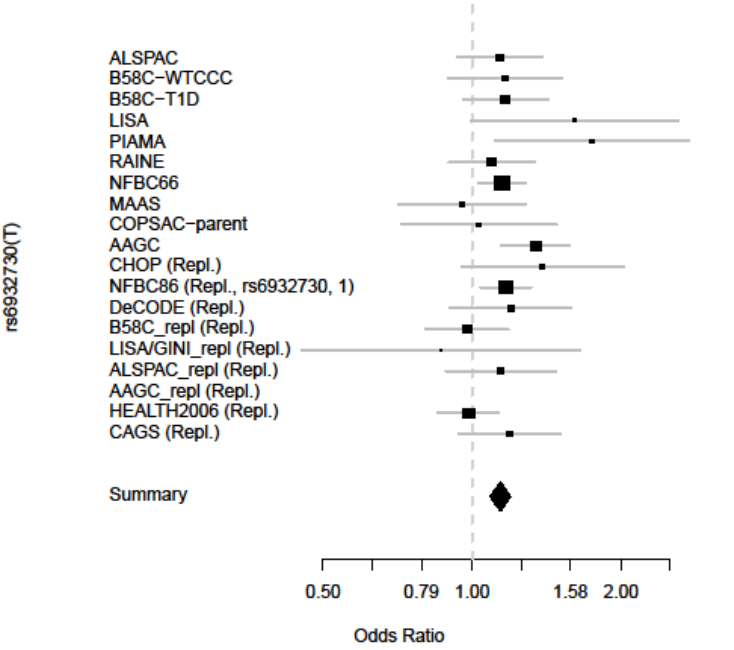
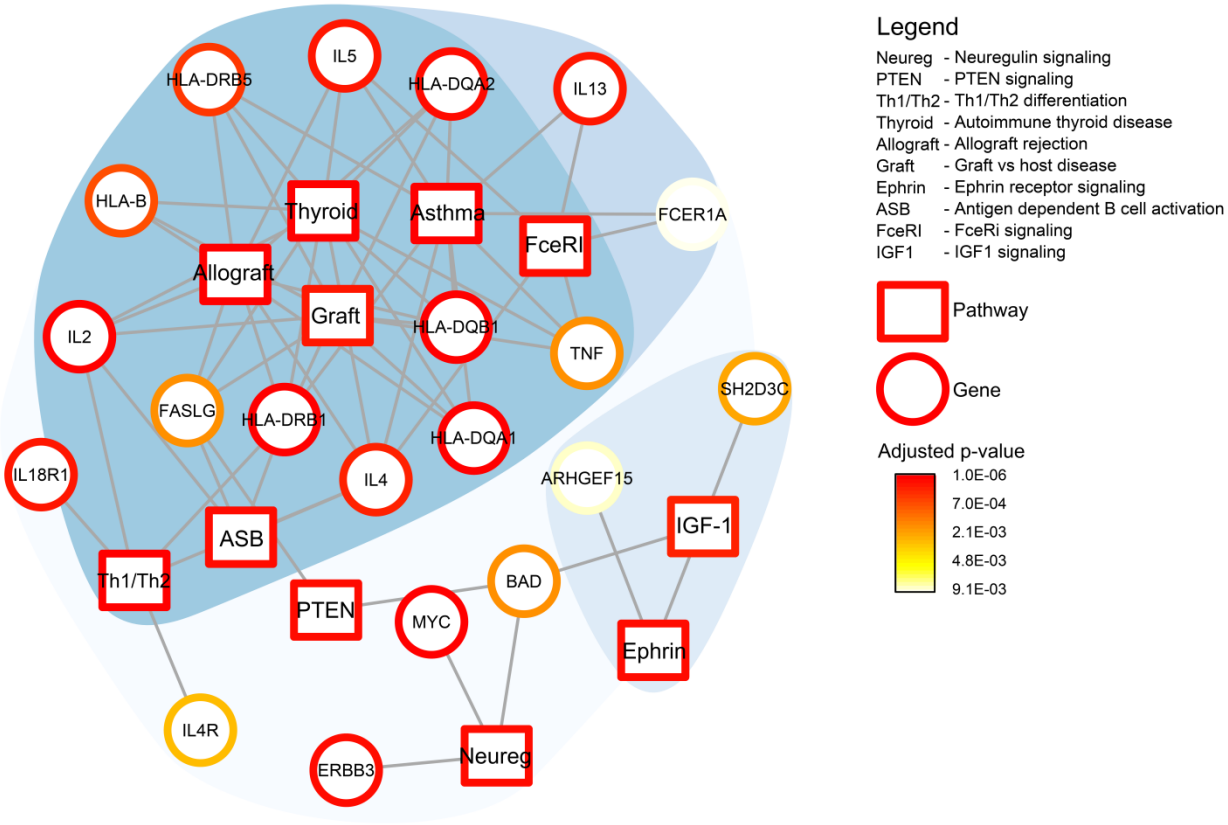
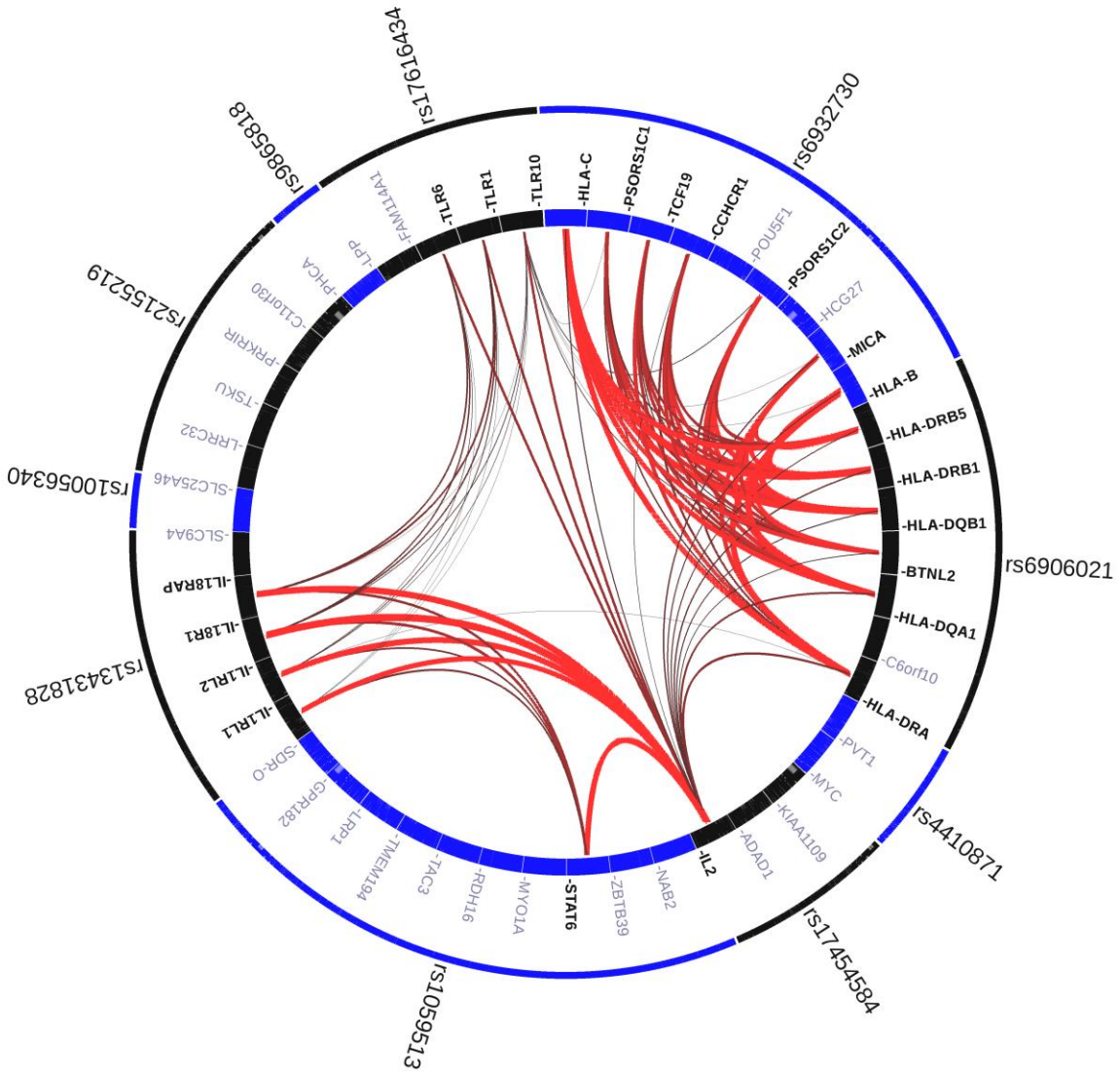
0.89
1.12
1.41
1.78
Odds Ratio


rs6932730(T)
ALSPAC
B58C−WTCCC
B58C−T1D
LISA
PIAMA
RAINE
NFBC66
MAAS
COPSAC−parent
AAGC
CHOP (Repl.)
NFBC86 (Repl., rs6932730, 1)
DeCODE (Repl.)
B58C_repl (Repl.)
LISA/GINI_repl (Repl.)
ALSPAC_repl (Repl.)
AAGC_repl (Repl.)
HEALTH2006 (Repl.)
CAGS (Repl.)
Summary
0.50
0.79
1.00
1.58
2.00
Odds Ratio

Supplementary Figure 4. Bipartite network of the most significant genes and gene sets identified using pathway enrichment analysis (MAGENTA). Individual genes associated with allergic sensitisation (Magenta gene score < 0.01) and involved in immune-related functions produced a cohesive cluster that is highlighted using a darker colour-coded shadow under them. Gene sets (pathway) and genes are depicted in squares and circles respectively.



Supplementary Figure 5. GRAIL analysis based on the 10 genome-wide significant loci



Supplementary Table 1 . Study characteristics - discovery & replication

Cohort	Cohort type	N (Genotype + phenotype) for main outcome	Phenotype (asthma) related criteria for genotyping	Percent male	Age	Method	Allergens tested for
Discovery							
AAGC	Population based	2719	Selected for asthma (1871 cases, 848 controls)	44%	mean 45 yr (7 - 90)	SPT	cockroach mixture (QIMR, CAPS), D. pteronyssinus (QIMR, LIWA, Busselton, TAHS, CAPS, MESCA), D. farinae (QIMR, Busselton), house dust (QIMR), cat dander (QIMR, LIWA, Busselton, TAHS, CAPS), dog dander (QIMR, LIWA, Busselton), Canary grass (QIMR), Timothy grass (QIMR), southern grasses mixture (QIMR), Rye grass (QIMR, Busselton, TAHS, CAPS, MESCA), Aspergillus spp. mixture (QIMR), Alternaria spp. mixture (QIMR), cows milk (QIMR, CAPS), egg white (QIMR, CAPS), egg yolk (CAPS), mould mixture (LIWA, Busselton), grass pollen mixture (LIWA), Alternaria tenuis (Busselton, TAHS, CAPS), Aspergillus fumigatus (Busselton, TAHS), grass mixture (Busselton), Cladosporium herbarum (TAHS), Penicillium spp. (TAHS), grass mixture (TAHS, CAPS), salmon (CAPS), tuna (CAPS), peanuts (CAPS)
ALSPAC	Birth cohort	2035	Selected for asthma 650 cases, 650 controls)	52%	7.5 yr	SPT	Dust mite, grass, cat, egg, peanut and mixed nuts
B58C (WTCCC)	Birth cohort	1320	None	50%	45 yr	Spec IgE (HYTEC)	Dust mite, mixed grass, cat
B58C (T1DGC)	Birth cohort	2267	None	47%	45 yr	Spec IgE (HYTEC)	Dust mite, mixed grass, cat
COPSAC parent	Parents of birth cohort	558	Selected for asthma (305 cases)	45%	20-45 yr	Spec IgE (ImmunoCAP)	Cat, dog, horse, birch, timothy grass, D. pteronyssinus, mugwort, cladosporium
LISA	Birth cohort	333	None	58%	6 & 10 yr	Spec IgE (RAST)	Inhalant mix (SX1): D. pteronyssinus, cat, dog, rye grass, timothy, cladosporium, birch, mugwort. Food mix (FX5): egg, peanuts, milk, codfish, wheat, soy.
MAAS	Birth cohort	813	None	54%	8, 11 yr	SPT+spec IgE (ImmunoCAP)	SPT: D. pteronyssinus, cat, dog, mixed grass, mixed trees, mixed moulds, milk, egg and peanut; latex (11yr only) SpecIgE: : House dust mite, cat, dog, timothy grass, milk, egg and peanut (age 8 years)

NFBC 1966	Birth cohort	4292	None	48%	31 yr	SPT	Cat, birch, timothy grass, D. pteronyssinus
PIAMA	Birth cohort	338	Selected for asthma (213 cases, 213 controls selected, genotypes available from 194 cases and 206 controls after quality check on gender and call rate)		8 yr	SPT+SpecIgE	D. pteronyssinus, D. farinae, Alternaria alternata, mixed grass pollen, mixed tree pollen, cat, and dog, milk and egg
RAINE	Birth cohort	1296	None	52%	6, 14 yr	SPT	Age 5/6: dust mite, cat, eggwhite, rye grass, moulds. Age 13/14: dust mite, cat, mould, peanut, rye grass, couch grass, grass mix
Replication **AAGC-replication**	Population based	2222	Selected for asthma (1210 cases, 1012 controls)	49%	Mean 47 (6-84)	SPT	Cockroach mixture (QIMR), D. pteronyssinus (QIMR, LIWA, COPD, MNCA, TAHS), D. farinae (QIMR), house dust (QIMR), cat dander (QIMR, LIWA, COPD, MNCA, TAHS), dog dander (QIMR, LIWA), Canary grass (QIMR), Timothy grass (QIMR), southern grasses mixture (QIMR), Rye grass (QIMR, COPD, MNCA, TAHS), Aspergillus spp. mixture (QIMR), Alternaria spp. mixture (QIMR), cows milk (QIMR, MNCA), egg white (QIMR, MNCA), mould mixture (LIWA), grass pollen mixture (LIWA), ragweed (COPD, MNCA), Cladosporium herbarum (COPD, MNCA, TAHS), Alternaria tenuis (COPD, MNCA, TAHS), Aspergillus fumigatus (COPD, MNCA, TAHS), Penicillium spp. (COPD, TAHS), wheat (MNCA), peanut mix (MNCA), shrimp (MNCA), grass mixture (TAHS)
ALSPAC-replication	Birth cohort	1683	None	49%	7.5 yrs	SPT	Dust mite, grass, cat, egg, peanut and mixed nuts
B58C-replication	Birth cohort	1906	None	50%	45 yr	Spec IgE (HYTEC)	Dust mite, mixed grass, cat
CAGS	Pediatric case control study	806	Selected for asthma	51%	6-18 yrs	SPT	D. pteronyssinus, cat dander, dog dander, birch, ragweed, mixed grass, egg, peanut

CHOP	Hospital based	574	None	51%	6-18 yr	SPT	Environmental (Alternaria tenuis; Hormodendrum cladospor.; Birch (Betula spp.); Oak (Quercus spp.); Ragweed (Ambrosia spp.); Grass mix; Timothy (Phleum); Alternaria tenuis; Hormodendrum cladospor.; Mold Mix; Birch (Betula spp.); Oak (Quercus spp.); Tree mix; Hickory (Carya); Maple (Acer, Red); Ragweed (Ambrosia spp.); Weed mix) and Food (Milk, Cow; Turkey; Barley; Corn; Oat; Rice; Egg; Apple; Soybean; Almond; Black Walnut; Brazil nut; Cashew; Pistachio; Pecan; Hazelnut; Walnut; Peanut; Wheat; White Potato; Carrot; Greenbean; Peas, Beef; Chicken; Oyster; Scallops; Shrimp; Catfish; Cod; Flounder; Mackerel; Lake Trout; Salmon; Tuna; Whitefish; Clam; Crab Mix; Lobster) allergen panels
deCODE	Population based	1250	Selected for asthma	33%	45 yr	SPT	12 common aeroallergens (Betula, Timotej, Cladosporium, Alternaria, Cat, Dog, Horse, rumex crispus, rumex acetocella, D. farina, D. pteronyssinus and Dandelion).
GINI/LISA-replication	Birth cohort	438	None	52%	6 & 10 yr	Spec IgE (RAST)	Inhalant mix (SX1): D. pteronyssinus, cat, dog, rye grass, timothy, cladosporium, birch, mugwort. Food mix (FX5): egg, peanuts, milk, codfish, wheat, soy.
Health2006	Adult cohort population based	3376	None	45%	18-69 yr (mean 49.4 yr)	Spec IgE + SPT	Spec IgE (grass, birch, cat, D. pteronyssinus) + SPT (grass, birch, mugwort, horse, dog, cat, D. farinae, D. pteronyssinus, Alternaria alternata, Cladosporium Herbarum)
NFBC 1986	Birth cohort	4454	None	49%	16 yr	SPT	Cat, birch, timothy grass, D. pteronyssinus

Supplementary Table 2. Case and control definitions and numbers

Discovery

Study	Phenotype	Case definition	Case numbers	Control definition	Control numbers
AAGC	Combined SPT 3mm and or specIgE 3.5 IU/mL	SPT 3 mm above negative control	1871	No SPT>= 1mm	848
	SPT 3mm	SPT 3 mm above negative control	1871	No SPT>= 1mm	848
	Spec IgE 3.5 IU/mL	NA	NA	NA	NA
ALSPAC	Combined SPT 3mm and or specIgE 3.5 IU/mL	SPT 3 mm above negative control	512	No SPT>= 1mm	1523
	SPT 3mm	SPT 3 mm above negative control	512	No SPT>= 1mm	1523
	Spec IgE 3.5 IU/mL	NA	NA	NA	NA
B58C (WTCCC)	Combined SPT 3mm and or specIgE 3.5 IU/mL	Spec IgE>=3.5 IU/mL	275	No spec IgE>=0.35 IU/mL	1045
	SPT 3mm	NA	NA	NA	NA
	Spec IgE 3.5 IU/mL	Spec IgE>=3.5 IU/mL	275	No spec IgE>=0.35 IU/mL	1045
B58C (T1DGC)	Combined SPT 3mm and or specIgE 3.5 IU/mL	Spec IgE>=3.5 IU/mL	475	No spec IgE>=0.35 IU/mL	1792
	SPT 3mm	NA	NA	NA	NA
	Spec IgE 3.5 IU/mL	Spec IgE>=3.5 IU/mL	475	No spec IgE>=0.35 IU/mL	1792
COPSAC parent	Combined SPT 3mm and or specIgE 3.5 IU/mL	Spec IgE>=3.5 IU/mL	211	No spec IgE>=0.35 IU/mL	283
	SPT 3mm	NA	NA	NA	NA
	Spec IgE 3.5 IU/mL	Spec IgE>=3.5 IU/mL	211	No spec IgE>=0.35 IU/mL	283
LISA	Combined SPT 3mm and or specIgE 3.5 IU/mL	Spec IgE>=3.5 IU/mL	70	No spec IgE>=0.35 IU/mL	263
	SPT 3mm	NA	NA	NA	NA
	Spec IgE 3.5 IU/mL	Spec IgE>=3.5 IU/mL	70	No spec IgE>=0.35 IU/mL	263
MAAS	Combined SPT 3mm and or specIgE 3.5 IU/mL	Spec IgE>=3.5 IU/mL and/or SPT 3 mm above negative control	319	No spec IgE>=0.35 IU/mL and/or no SPT >= 1mm	441
	SPT 3mm	SPT 3 mm above negative control	315	-	441
	Spec IgE 3.5 IU/mL	Spec IgE>=3.5 IU/mL	147	-	441
NFBC 1966	Combined SPT 3mm and or specIgE 3.5 IU/mL	SPT 3 mm above negative control	1334	No SPT>= 3mm	3102
	SPT 3mm	SPT 3 mm above negative control	1334	No SPT>= 3mm	3102
	Spec IgE 3.5 IU/mL	NA	NA	NA	NA
PIAMA	Combined SPT 3mm and or specIgE 3.5 IU/mL	Spec IgE>=3.5 IU/mL and/or SPT 3 mm above negative control	104	No spec IgE>=0.35 IU/mL and/or no SPT >= 1mm	176
	SPT 3mm	SPT 3 mm above negative control	52	-	176
	Spec IgE 3.5 IU/mL	Spec IgE>=3.5 IU/mL	98	-	176

RAINE	Combined SPT 3mm and or specIgE 3.5 IU/mL	SPT 3 mm above negative control	618	No SPT>= 1mm	583
	SPT 3mm	SPT 3 mm above negative control	618	No SPT>= 1mm	583
	Spec IgE 3.5 IU/mL	NA	NA	NA	NA
Replication					
AAGC-replication	Combined SPT 3mm and or specIgE 3.5 IU/mL	SPT 3 mm above negative control	1210	No SPT>= 1mm	1012
	SPT 3mm	SPT 3 mm above negative control	1210	No SPT>= 1mm	1012
	Spec IgE 3.5 IU/mL	NA	NA	NA	NA
ALSPAC-replication	Combined SPT 3mm and or specIgE 3.5 IU/mL	SPT 3 mm above negative control	292	No SPT>= 1mm	1391
	SPT 3mm	SPT 3 mm above negative control	292	No SPT>= 1mm	1391
	Spec IgE 3.5 IU/mL	NA	NA	NA	NA
B58C-replication	Combined SPT 3mm and or specIgE 3.5 IU/mL	Spec IgE>=3.5 IU/mL	435	No spec IgE>=0.35 IU/mL	1471
	SPT 3mm	NA	NA	NA	NA
	Spec IgE 3.5 IU/mL	Spec IgE>=3.5 IU/mL	435	No spec IgE>=0.35 IU/mL	1471
CAGS	Combined SPT 3mm and or specIgE 3.5 IU/mL	NA	441	No SPT>= 1mm	365
	SPT 3mm	SPT 3mm above negative control	441	No SPT>= 1mm	365
	Spec IgE 3.5 IU/mL	NA	NA	NA	NA
CHOP	Combined SPT 3mm and or specIgE 3.5 IU/mL	SPT 3 mm above negative control	393	No SPT>= 3mm	181
	SPT 3mm	SPT 3 mm above negative control	393	No SPT>= 3mm	181
	Spec IgE 3.5 IU/mL	NA	NA	NA	NA
decode	Combined SPT 3mm and or specIgE 3.5 IU/mL	SPT 3 mm above negative control or >50% of the histamine control	953	No SPT>=1mm	297
	SPT 3mm	SPT 3 mm above negative control	953	No SPT>= 1mm	297
	Spec IgE 3.5 IU/mL	NA	NA	NA	NA
GINI/LISA	Combined SPT 3mm and or specIgE 3.5 IU/mL	Spec IgE>=3.5 IU/mL	41	No spec IgE>=0.35 IU/mL	397
	SPT 3mm	NA	NA	NA	NA
	Spec IgE 3.5 IU/mL	Spec IgE>=3.5 IU/mL	41	No spec IgE>=0.35 IU/mL	397
Health2006	Combined SPT 3mm and or specIgE 3.5 IU/mL	Spec IgE>=3.5 IU/mL and/or SPT 3 mm above negative control	850	No spec IgE>=0.35 IU/mL and/or no SPT >= 1mm	2279
	SPT 3mm	SPT 3 mm above negative control	688	No SPT>=1mm	1518
	Spec IgE 3.5 IU/mL	Spec IgE>=3.5 IU/mL	488	No spec IgE>=0.35 IU/mL and/or no SPT >= 1mm	2279
NFBC 1986	Combined SPT 3mm and or specIgE 3.5 IU/mL	SPT 3 mm above negative control	1499	No SPT>= 1mm	2527
	SPT 3mm	SPT 3 mm above negative control	1499	No SPT>= 1mm	2527
	Spec IgE 3.5 IU/mL	NA	NA	NA	NA

Supplementary Table 3. Study genetic & analysis methods

(a)

	Genotyping		BEFORE IMPUTATION QUALITY CONTROL PER SUBJECT				BEFORE IMPUTATION QUALITY CONTROL PER SNP				IMPUTATION			DATA ANALYSIS
Cohort	Genotyping Platform	Genotype-Calling Algorithm	call rate threshold	heterozygosity thresholds	ethnicity exclusions	other exclusion criteria	SNP call rate	HWE p-value threshold	MAF threshold	other exclusion criteria	Imputation Software (Version)	HapMap CEU Release	NCBI Build	Association Software
Discovery														
AAGC	Illumina 370K (n=55) or 610k (n=2664)	Illumina BeadStudio	0.95	no	caucasians only	sex discrepancies, related individuals	0.95	1 E-06	0.01	Allele frequency differences (P<0.001) between genotyping projects, inconsistent strand compared to HapMap	IMPUTE v2	1000G March 2010 + HM3 February 2009	36	PLINK
ALSPAC	Illumina 317K or 610k	Illumina BeadStudio	0.97	0.34 & 0.36	MDS - eigenstrat adjusted	sex discrpeancies, related individuals	0.97	5 E-07	0.005	no	MACH 1.0	22	36	MACH2DAT
B58C WTCCC	Affymetrix 500	Chiamo	0.97	0.225 & 0.3	caucasians only	external discordance, relatives,sex discrepancies	0.95 or (MAF< 0.05 & SNP call rate < 0.99).	5.7 E-07	0.01	Trend test for association for 58BC vs NBS p-value < 5.7E-07	IMPUTE	21	35	quicktest
B58C T1DGC	Illumina Infinium 550	Illuminus	0.97	0.29 & 0.34	caucasians only	external discordance, relatives, sex discrepancies	0.95	1 E-07	0.01	no	MACH	21	35	probAbel
COPSAC	Illumina 550K	BeadStudio v 3.3.4	0.98	no	caucasians only	no	0.95	1 E-04	0.01	no	IMPUTE v2	22	36	SNPTEST
LISA	Affymetrix 5.0	BRLMM-P	0.95	no	caucasians only	no	0.95	1 E-05	0.01	no	IMPUTE v1.06	22	36	SNPTEST
MAAS	Illumina 610 Quad array	Illumina BeadStudio	0.97	0.325	caucasians only	one of each sibling excluded	0.95	5.9 E-07	0.005	no	IMPUTE v2	22	36	SNPTEST
NFBC 1966	Illumina HumanCNV-370DUO Analysis BeadChip	Illumina BeadStudio	0.95	no	no	Concordance with another DNA >0.99; Contaminated samples: IBS pairwise with most other samples>0.99; IBS pairwise sharing >0.20; Withdrew consent; Gender discrepancies.	0.95 (0.99 for MAF<0.05)	1 E-04	0.01	no	IMPUTE v0.3.1	21	35	SNPTEST
PIAMA	Illumina Human610 quad array	Illumina BeadStudio	0.95	no	caucasians only (reported)	inconsistent sex	0.95	1 E-07	0.01	no	IMPUTE v2	22	36	SNPTEST
RAINE	Illumina 660K	Illumina Beadstudio	0.95	0.32 & 0.36	Eigenstrat adjusted	yes - IBD check and exclude family relations, sex descrepancies	0.95	5.7 E-07	0.01	no	MACH	22	36	MACH2DAT
Replication in silico														
B58C	Illumina 550K/610K	Beadstudio	0.97	no	caucasians only	no	0.95	1 E-04	0.01	no	MACH	21	35	probAbel
ALSPAC	Illumina HumanHap550 quad	Illumina BeadStudio	0.97	0.32 - 0.345 or 0.0.9731 - 0.33	caucasians only	sex discrepancies, cryptic relatedness, replicates <80% IBD	0.95	5 E-07	0.01	no	Mach 1.0.16	22	36	MACH2DAT
CHOP	Illumina HH 550v1/v3 HH610	Illumina BeadStudio	0.98	no	caucasians only	cryptic relatedness assessed by IBD	0.95	1 E-04	0.01	no	IMPUTE v2	22	36	SNPTEST
deCODE	Illumina HumanHap 300K/370K	Illumina BeadStudio	0.98	no	caucasians only	NA	0.95	1 E-06	0.01	no	IMPUTE v2	1000 G, Aug 2010	37	SNPTEST
GINI/LISA	Affymetrix 5.0 Affymetrix 6.0	BRLMM-P (5.0), BIRDSEED V2 (6.0)	0.95	Mean +/- 4 SD	caucasians only	sex discrepancies	0.95	1 E-05	0.01	no	IMPUTE v2	22	36	SNPTEST
NFBC 1986	Illumina Metabochip	GenCall	0.95	abs(F)>0.05	caucasians only (reported)	non-consent, sex discepenacies, cryptic relatedness, parents	0.95 if MAF>5%, 0.99 if 1<MAF<5%	no	no	no	NA	NA	NA	PLINK

(b)	Genotyping		QUALITY CONTROL PER SUBJECT			QUALITY CONTROL PER SNP			DATA ANALYSIS
Cohort	Genotyping Method	Genotype-Calling Algorithm	call rate threshold	ethnicity exclusions	other exclusion criteria	lowest SNP call rate	SNPs with HWE p-values <0.05	MAF threshold	Association Software
Replication de novo									
AAGC-replication	Sequenom MassArray	Sequenom	0.98	caucasians only (reported)	Sexdisrepancies	0.98	1	NA	PLINK
CAGS	sequenom and taqman		0.97	caucasians only	no	0.97	2 out of 26	0.09	SNPTEST
Health2006	The PCR KASPar genotyping system (KBiosciences, Hoddesdon, UK).	Kraken-Kbioscience	0.985	caucasians only (reported)	non-Danish citizenship, not born in Denmark	0.98	2 out of 15	0.1	SPSS

Supplementary Table 4. Discovery and replication results of the 26 top loci from the discovery analysis

						Discovery (stage 1)			Replication (stage2)		Combined		
Region	SNP	Position (bp)	Nearest gene	Eff allele	Alt allele	Effect allele freq.	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	Het *P*/ I^2 (%)
Top loci from discovery analysis replicating in stage 2 and genome wide significant in the combined analysis													
11q13.5	rs2155219	75976842	*C11orf30*	t	g	0.47	1.20 (1.14-1.24)	**1.8E-12**	1.15 (1.09-1.21)	1.1E-07	1.18 (1.13-1.22)	**1.4E-18**	0.57/0
12q13.3	rs1059513	55775976	*STAT6*	t	c	0.90	1.34 (1.22-1.47)	**1.6E-10**	1.24 (1.13-1.37)	1E-05	1.30 (1.21-1.39)	**1.0E-14**	0.25/17
5q22.1	rs10056340	110217951	*SLC25A46*	t	g	0.83	0.82 (0.77-0.88)	**3.2E-09**	0.83 (0.77-0.90)	4.4E-06	0.83 (0.78-0.87)	**5.2E-14**	0.93/0
6p21.32	rs6906021	32734289	*HLADQB1*	t	c	0.55	0.86 (0.82-0.91)	**1.3E-08**	0.87 (0.81-0.93)	4.8E-05	0.87 (0.83-0.90)	**2.2E-12**	0.51/0
2q12.1	rs3771175	102326642	*IL1RL1/IL18R1*	a	t	0.14	0.79 (0.72-0.88)	9.1E-06	0.83 (0.77-0.90)	1.1E-06	0.83 (0.78-0.88)	**4.9E-11**	0.39/5
4p14	rs17616434	38489271	*TLR1/6/10*	t	c	0.78	1.24 (1.16-1.32)	**3.8E-11**	1.22 (1.15-1.31)	3.8E-10	1.23 (1.18-1.29)	**5.2 E-11***	0.04/40
3q28	rs9865818	189555207	*LPP*	a	g	0.59	0.88 (0.84-0.93)	3.4E-06	0.90 (0.85-0.94)	2.2E-05	0.89 (0.86-0.92)	**2.7E-10**	0.49/0
8q24.21	rs4410871	128884211	*MYC/PVT1*	t	c	0.28	1.16 (1.09-1.23)	2.0E-07	1.12 (1.05-1.20)	6.7E-04	1.14 (1.09-1.19)	**5.4E-10**	0.45/1
4q27	rs17454584	123572882	*IL2/ADAD1*	a	g	0.74	0.88 (0.83-0.93)	9.5E-06	0.86 (0.80-0.92)	1.4E-05	0.87 (0.83-0.91)	**5.5E-10**	0.74/0
6p21.33	rs6932730	31462161	*HLA-B/MICA*	t	c	0.82	1.18 (1.10-1.26)	7.9E-07	1.10 (1.02-1.18)	0.0075	1.14 (1.09-1.20)	**4.2E-08**	0.26/16
Top loci from discovery analysis not replicating in stage2													
2q13	rs11122895	112186626	*ANAPC1*	t	c	0.39	1.14 (1.08-1.20)	9.4E-07	1.05 (1.00-1.10)	0.062	1.09 (1.05-1.13)	1.5E-06	
6p12.1	rs16887812	56318723	*COL21A1*	t	c	0.35	1.13 (1.07-1.20)	2.8E-06	1.04 (0.98-1.11)	0.17	1.10 (1.05-1.14)	6.7E-06	
1q24.3	rs859624	170997452	*FASLG*	t	c	0.24	1.14 (1.08-1.21)	5.1E-06	1.03 (0.95-1.12)	0.43	1.10 (1.05-1.16)	2.7E-05	
6q15	rs9294385	88450677	*ORCL3/AKIRIN2*	a	c	0.27	1.15 (1.08-1.22)	1.7E-06	1.02 (0.96-1.10)	0.48	1.09 (1.05-1.14)	3.3E-05	
2q12.1	rs6759479	102406479	*IL18RAP/SLC9A4*	a	c	0.50	1.12 (1.06-1.18)	8.3E-06	1.03 (0.97-1.09)	0.30	1.08 (1.04-1.12)	4.8E-05	
6q14.1	rs9344121	81959006		t	g	0.76	0.87 (0.82-0.93)	6.8E-06	0.99 (0.91-1.07)	0.72	0.91 (0.87-0.95)	9.3E-05	
16p12.1	rs9937695	25861972	*HS3ST4*	a	g	0.60	0.89 (0.84-0.93)	3.9E-06	0.99 (0.92-1.06)	0.76	0.92 (0.88-0.96)	9.3E-05	
12p13.31	rs3181295	6214435	*CD9*	a	g	0.42	1.12 (1.07-1.18)	7.8E-06	1.01 (0.96-1.07)	0.65	1.07 (1.03-1.11)	3.1E-04	
5q35.1	rs1469066	169498622		t	c	0.62	0.89 (0.84-0.93)	3.9E-06	1.01 (0.94-1.09)	0.71	0.93 (0.89-0.97)	3.6E-04	
18q12.2	rs7350983	35222815		t	c	0.90	0.82 (0.75-0.89)	5.4E-06	0.99 (0.90-1.09)	0.81	0.89 (0.83-0.95)	3.6E-04	
4p16.1	rs12511580	10838566		a	g	0.33	1.14 (1.07-1.21)	8.7E-06	0.99 (0.92-1.07)	0.82	1.08 (1.03-1.14)	5.1E-04	
22q13.32	rs5771884	47432785	*FAM19A5*	t	c	0.20	0.86 (0.80-0.91)	1.9E-06	1.01 (0.94-1.08)	0.83	0.92 (0.88-0.97)	5.2E-04	
15q14	rs12912542	36787551	*C15orf53*	a	c	0.71	0.88 (0.83-0.93)	8.2E-06	1.03 (0.95-1.11)	0.50	0.93 (0.89-0.97)	0.0012	
5q34	rs2961919	159835712	*SLU7*	a	g	0.68	1.14 (1.08-1.21)	1.8E-06	0.97 (0.91-1.03)	0.33	1.07 (1.02-1.11)	0.0023	
3p24.3	rs6807490	20936645		a	c	0.85	0.84 (0.78-0.91)	4.8E-06	1.02 (0.94-1.11)	0.58	0.92 (0.87-0.97)	0.0023	
6p24.3	rs12201441	10006680	*OFCC1*	a	g	0.34	0.87 (0.82-0.92)	4.2E-06	1.07 (1.00-1.15)	0.049	0.95 (0.91-1.00)	0.029	

P value for discovery and combined analysis is in bold if genome-wide significant ($P < 5 \times 10^{-8}$)

Het *P*: Heterogeneity *P* for Cochrane's Q statistic

* The *P* value was calculated by random effects model due to evidence of heterogeneity between studies (Heterogeneity *P* for Cochrane's Q statistic < 0.05, $I^2 > 25\%$)

Supplementary table 5. Replication of top loci from the sensitization analysis in an independent study on allergic symptoms

The replication study[1] comprised samples from the 23andMe study (N=46,646) and parents from the ALSPAC cohort (parents, N=7,216). Since children from the ALSPAC cohort participated in the sensitization meta-analysis this is not a completely independent analysis, and a sensitivity analysis was performed by stratified analyses only including the 23andMe-sample, showing similar strength of association (*P* value 23andMe).

				Allergic sensitizations Current meta-analysis		**Allergic symptoms Replication**		
Region	**SNP**	**Nearest gene**	**Eff allele**	**OR (95% CI)**	***P* value**	**OR**	***P* value 23andMe**	***P* value 23andMe + ALSPAC parents**
11q13.5	rs2155219	*C11orf30*	t	1.18 (1.13-1.22)	1.4E-18	1.11	**2.5E-16**	**1.5E-19**
12q13.3	rs1059513	*STAT6*	t	1.30 (1.21-1.39)	1.0E-14	1.06	**0.003**	**0.004**
5q22.1	rs10056340	*SLC25A46*	t	0.83 (0.78-0.87)	5.2E-14	0.91	**2.6E-08**	**2.2E-09**
6p21.32	rs6906021	*HLADQB1*	t	0.87 (0.83-0.90)	2.2E-12	0.91	**3.4E-13**	**7.9E-15**
2q12.1	rs3771175	*IL1RL1/IL18R1*	a	0.83 (0.78-0.88)	4.9E-11	0.87	**9.8E-14**	**1.7E-15**
4p14	rs17616434	*TLR1/6/10*	t	1.23 (1.18-1.29)	5.2E-11	1.14	**1.3E-10**	**2.4E-20**
3q28	rs9865818	*LPP*	a	0.89 (0.86-0.92)	2.7E-10	0.94	**9.7E-07**	**2.2E-07**
8q24.21	rs4410871	*MYC/PVT1*	t	1.14 (1.09-1.19)	5.4E-10	1.04	**0.0047**	**0.001**
4q27	rs17454584	*IL2/ADAD1*	a	0.87 (0.83-0.91)	5.5E-10	0.93	**1.7E-06**	**1.5E-07**
6p21.33	rs6932730	*HLA-B/MICA*	t	1.14 (1.09-1.20)	4.2E-08	1.07	1.0 E-04	**3.9 E-05**

P value for replication is in bold if significantly associated after Bonferroni correction for the 10 genome-wide significant loci ($P < 0.005$)

Supplementary Table 6. Analyses of association between top SNP and expression of genes located in a distance +/- 1 mb distance in 4 different tissues

SNPxGENE results with *P* <0.001 in at least one study

		Alleles		deCODE: white blood cells			deCODE: adipose tissue			ALSPAC: LCLs				KORA: whole blood			
SNP	GENE	Effect	Other	BETA	SE	PVALUE	BETA	SE	PVALUE	BETA	SE	PVALUE	R2	BETA	SE	PVALUE	R2
rs10056340	*CAMK4*	T	G	NA	NA	NA	NA	NA	NA	-0.214	0.063	**0.0007**	0.012	0.003	0.012	0.8017	0.039
rs1059513	*TMEM194A*	T	C	0.167	0.081	0.0470	0.328	0.092	**0.0006**	NA	NA	NA	NA	NA	NA	NA	NA
rs1059513	*NAB2_STAT6*	T	C	0.260	0.081	0.0018	0.473	0.091	**4.7e-07**	NA	NA	NA	NA	NA	NA	NA	NA
rs1059513	*NACA*	T	C	0.059	0.083	0.4900	0.338	0.091	**0.0004**	-0.181	0.071	0.0110	0.007	-0.113	0.086	0.1880	0.009
rs1059513	*STAT6*	T	C	NA	NA	NA	NA	NA	NA	0.430	0.070	**7.6E-10**	0.039	0.188	0.043	**1.6E-05**	0.027
rs17616434	*AK023259*	T	C	-0.252	0.060	**4.4E-05**	-0.230	0.065	**0.0006**	NA	NA	NA	NA	NA	NA	NA	NA
rs17616434	*FAM114A1*	T	C	-0.306	0.058	**2.7E-07**	-0.283	0.066	**3.7E-05**	-0.400	0.053	**3.5E-14**	0.057	0.000	0.007	0.9838	0.006
rs17616434	*TLR1*	T	C	0.234	0.061	**0.0002**	0.139	0.067	0.0440	-0.212	0.053	**7.1E-05**	0.016	-0.035	0.055	0.5235	0.003
rs17616434	*TLR10*	T	C	0.070	0.060	0.2500	0.044	0.067	0.5200	-0.569	0.051	**2.8E-29**	0.118	0.052	0.010	**1.7E-07**	0.047
rs17616434	*TLR6*	T	C	0.281	0.059	**4.1E-06**	0.034	0.066	0.6200	-0.706	0.049	**7.5E-48**	0.183	0.046	0.021	0.0259	0.022
rs2155219	*C11orf30*	T	G	-0.577	0.053	**4.2E-26**	-0.476	0.058	**2.2E-15**	NA	NA	NA	NA	NA	NA	NA	NA
rs2155219	*LRRC32*	T	G	-0.252	0.054	**7.1E-06**	0.070	0.061	0.2700	-0.083	0.048	0.0835	0.003	-0.016	0.007	0.0236	0.007
rs3771175	*IL18RAP*	T	A	-0.551	0.082	**6.2E-11**	0.183	0.088	0.0450	0.102	0.070	0.1461	0.002	-0.335	0.044	**7.3E-14**	0.077
rs3771175	*MFSD9*	T	A	-0.465	0.083	**5.4E-08**	0.022	0.091	0.8200	-0.063	0.070	0.3722	0.001	-0.035	0.014	0.0129	0.009
rs6906021	*GPSM3_NOTCH4*	T	C	0.087	0.054	0.1200	0.399	0.060	**1.8E-10**	NA	NA	NA	NA	NA	NA	NA	NA
rs6906021	*HLA-DPB1*	T	C	-0.260	0.056	**7.5E-06**	-0.273	0.062	**2.2E-05**	-0.106	0.046	0.0222	0.006	-0.062	0.023	0.0086	0.013
rs6906021	*HLA-DQA1*	T	C	0.864	0.045	**2.5E-77**	0.704	0.056	**3.1E-34**	0.397	0.045	**5.9E-19**	0.077	0.455	0.031	**5.1E-42**	0.224
rs6906021	*HLA-DQA2*	T	C	-0.110	0.057	0.0640	-0.061	0.063	0.3500	-0.183	0.046	**8.1E-05**	0.016	-0.013	0.008	0.1097	0.011
rs6906021	*HLA-DQB1*	T	C	0.758	0.047	**9.7E-55**	0.390	0.061	**8.2E-10**	NA	NA	NA	NA	-0.920	0.036	**3.4E-104**	0.472
rs6906021	*HLA-DQB2*	T	C	0.256	0.054	**5.1E-06**	0.154	0.062	0.0180	NA	NA	NA	NA	0.029	0.011	0.0082	0.012
rs6906021	*HLA-DRB1*	T	C	NA	NA	NA	NA	NA	NA	0.552	0.043	**5.9E-38**	0.149	NA	NA	NA	NA
rs6906021	*HLA-DRB1_HLA-DRB5*	T	C	0.396	0.054	**1.4E-12**	0.503	0.060	**6.7E-16**	NA	NA	NA	NA	NA	NA	NA	NA
rs6906021	*HLA-DRB1_HLA-DRB5_HLA-DRB6*	T	C	-0.427	0.055	**5.2E-14**	-0.273	0.062	**2.2E-05**	NA	NA	NA	NA	NA	NA	NA	NA
rs6906021	*HLA-DRB5*	T	C	0.411	0.053	**4.6E-14**	0.416	0.061	**5.9E-11**	0.341	0.045	**3.9E-14**	0.057	-0.172	0.021	**9.3E-16**	0.088
rs6906021	*HSPA1B*	T	C	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.085	0.024	**0.0004**	0.022
rs6906021	*PSMB9*	T	C	-0.253	0.056	**1.2E-05**	-0.158	0.062	0.0140	-0.192	0.046	**3.3E-05**	0.018	-0.043	0.026	0.0965	0.026
rs6906021	*TAP2*	T	C	0.059	0.057	0.3200	-0.168	0.063	0.0093	-0.345	0.045	**2.2E-14**	0.058	-0.079	0.019	**2.3E-05**	0.027
rs6932730	*APOM*	T	C	-0.169	0.077	0.0340	-0.341	0.083	**7.8E-05**	NA	NA	NA	NA	-0.009	0.012	0.4498	0.004
rs6932730	*C5orf13*	T	C	NA	NA	NA	NA	NA	NA	-0.249	0.065	**0.0001**	0.016	NA	NA	NA	NA
rs6932730	*HLA-B_HLA-C_HLA-Cw*050x*	T	C	-0.288	0.076	**0.0002**	-0.218	0.084	0.0120	NA	NA	NA	NA	NA	NA	NA	NA

rs6932730	*HLA-C*	T	C	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.411	0.059	**5.7E-12**	0.063
rs6932730	*HSPA1B*	T	C	0.205	0.081	0.0140	0.494	0.082	**4.7E-09**	NA	NA	NA	NA	-0.001	0.029	0.9812	0.005
rs6932730	*IER3*	T	C	NA	NA	NA	NA	NA	NA	-0.260	0.064	**4.4E-05**	0.017	0.047	0.032	0.1402	0.006
rs6932730	*LST1*	T	C	0.011	0.078	0.8900	-0.079	0.085	0.3800	-0.313	0.064	**9.1E-07**	0.025	0.038	0.025	0.1384	0.025
rs6932730	*MICB*	T	C	0.516	0.075	**2.3E-11**	0.514	0.083	**2.4E-09**	NA	NA	NA	NA	0.076	0.027	0.0044	0.017
rs6932730	*NEU1*	T	C	0.172	0.078	0.0340	0.025	0.085	0.7800	0.219	0.065	**0.0008**	0.012	0.001	0.019	0.9784	0.022
rs6932730	*TAP2*	T	C	NA	NA	NA	NA	NA	NA	-0.284	0.065	**1.1E-05**	0.02	NA	NA	NA	NA
rs6932730	*VARS2*	T	C	NA	NA	NA	NA	NA	NA	-0.223	0.064	**0.0005**	0.013	-0.042	0.025	0.0950	0.004

Supplementary Table 7. Analyses of association between top SNPs and expression of genes located in a distance +/- 1 mb distance in B-cells and monocytes. Based on data from Fairfax et al. Nat Genet 2012; 44(5): 502-510.

SNPxGENE results with a P<0.01 in B-cells and/or monocytes

			B-cells		Monocytes	
SNP	GENE	Probe	Allelic_expression _direction	*P* VALUE	Allelic_expression _direction	*P* VALUE
rs17616434	*HS.214235*	2120056	-	-	C>T	0.002
rs1059513	*CYP27B1*	2900725	T>C	0.003	-	-
rs1059513	*STAT6*	1660397	T>C	0.007	T>C	6.4 E-05
rs1059513	*RNF41*	1090433	-	-	T>C	0.007
rs1059513	*STAT2*	130519	-	-	T>C	0.008
rs17454584	*IL2*	4290356	G>A	0.002	-	-
rs6906021	*HSPA1B*	3850433	C>T	3.9 E-04	-	-
rs6906021	*TAP2*	3940477	C>T	0.002	C>T	4.8 E-04
rs6906021	*ATF6B*	4640110	C>T	0.004	-	-
rs6906021	*VARS*	6980100	T>C	0.009	-	-
rs6906021	*BRD2*	1340475	-	-	C>T	0.007
rs6906021	*CLIC1*	3450072	-	-	C>T	0.007
rs3771175	*IL1R1*	240274	A>T	0.001	-	-
rs9865818	*LPP*	6350711	G>A	4.0 E-06	-	--
rs9865818	*LPP*	2760309	G>A	7.3 E-06	-	-

Supplementary Table 8. Variants associated ($P < 10^{-5}$) with gene expression levels (eQTL) and in LD ($r^2 > 0.5$) with the 10 top SNPs identified in the EAGLE sensitization GWAS. Based on publically available data from the GHS-Express database of Zeller et al. PLoS One 2010. 5, e10693.

Top SNP	SNP in LD	r2 with the top SNP	CHR	POS (hg18)	Minor Allele	Major Allele	MAF	In Gene	eQTL Gene(s)	Lowest eQTL *P* value
rs1059513	rs10506348	0.56	12	55617637	G	A	0.09		*STAT6*	5.19E-13
rs17454584	rs17388568	0.74	4	123548812	A	G	0.30	*ADAD1*	*HBEGF*	3.51E-06
rs17454584	rs925549	0.55	4	123750443	C	T	0.34		*HBEGF*	4.66E-06
rs17454584	rs6829845	0.54	4	123730216	A	G	0.34		*HBEGF*	9.88E-06
rs17616434	rs2101521	0.91	4	38487946	A	G	0.22		*RPL32P3,TLR6*	8.32E-07
rs17616434	rs6835514	0.80	4	38570775	G	A	0.25	*FAM114A1*	*TLR6*	5.70E-07
rs17616434	rs5743592	0.72	4	38479458	G	A	0.19	*TLR1*	*DNAJC7,RPL32P3,TLR6*	1.37E-08
rs17616434	rs11722813	0.72	4	38487164	T	C	0.19		*DNAJC7,RPL32P3,TLR6*	1.89E-08
rs17616434	rs17582830	0.66	4	38543822	G	A	0.21		*DNAJC7,TLR6,ZNF236*	3.31E-07
rs17616434	rs11466640	0.63	4	38455298	A	G	0.18	*TLR10*	*DNAJC7,TLR6*	1.64E-07
rs17616434	rs11096956	0.55	4	38452575	A	C	0.22	*TLR10*	*TLR6*	5.64E-07
rs3771175	rs3771158	0.74	2	102376326	G	A	0.18	*IL18R1*	*NPAT*	5.00E-06
rs3771175	rs10197310	0.71	2	102386462	A	T	0.18		*NPAT*	2.46E-06
rs3771175	rs10210176	0.71	2	102445948	A	C	0.18		*NPAT*	3.06E-06
rs3771175	rs11687768	0.71	2	102392170	G	A	0.18		*NPAT*	4.91E-06
rs3771175	rs10202813	0.71	2	102386172	T	G	0.18		*NPAT*	7.58E-06
rs6932730	rs2394999	0.74	6	31508914	G	A	0.20		*COL7A1,HCG4,MICB*	4.37E-07
rs6932730	rs4081552	0.67	6	31461668	A	G	0.31		*HLA-C,HLA-DQB1,MICB*	1.01E-08
rs6932730	rs16899646	0.51	6	31524899	G	C	0.15		*HCG4*	1.16E-07
rs9865818	rs2030516	0.85	3	189584433	T	C	0.43	*LPP*	*BCL6*	5.17E-09
rs9865818	rs9864529	0.79	3	189587750	G	A	0.45	*LPP*	*BCL6*	5.22E-10
rs9865818	rs7640550	0.79	3	189562942	T	C	0.46	*LPP*	*BCL6*	5.51E-09
rs9865818	rs2030520	0.75	3	189602276	C	T	0.45	*LPP*	*BCL6,SDSL*	1.12E-09
rs9865818	rs6780858	0.72	3	189614804	G	A	0.47	*LPP*	*BCL6*	2.09E-06
rs9865818	rs13079741	0.68	3	189584555	G	C	0.49	*LPP*	*BCL6*	1.56E-06
rs9865818	rs1035766	0.51	3	189603434	A	G	0.46	*LPP*	*BCL6*	3.10E-07
rs9865818	rs1035765	0.51	3	189603477	T	A	0.46	*LPP*	*BCL6*	5.37E-07

Supplementary Table 9. Variants located within predicted regulatory regions and in LD (r^2 > 0.8) with the top SNPs in ten loci identified in the EAGLE sensitization GWAS

Top SNP	SNP in LD	r2 with the top SNP	CHR	POS (hg18)	Minor Allele	Major Allele	MAF	Function	Gene	Promoter histone marks	Enhancer histone marks	DNAse
rs3771175	rs72998585	0.82	2	102224922	T	A	0.155	Near-gene	*IL1RL2* (+2.7kb)		HMEC, NHEK	13 cell types
rs3771175	rs10189629	0.83	2	102245896	A	C	0.152	Near-gene	*IL1RL2* (+23.7kb)			13 cell types
rs3771175	rs11690644	0.94	2	102280646	G	A	0.140	Near-gene	*IL1RL1* (-13.7kb)			HCFaa,HMEC
rs3771175	rs950881	0.98	2	102298944	T	G	0.143	Intron	*IL1RL1*		Huvec, NHEK	5 cell types
rs3771175	rs3771180	0.99	2	102320049	T	G	0.144	Intron	*IL1RL1*		HMEC, Huvec, NHEK	28 cell types
rs3771175	rs72823646	0.99	2	102320645	A	G	0.144	Intron	*IL1RL1*		Huvec, NHEK	7 cell types
rs3771175	rs13431828	0.99	2	102321085	T	C	0.144	UTR-5	*IL1RL1*		Huvec, NHEK	11 cell types
rs3771175	rs13408569	0.99	2	102321488	C	G	0.144	Intron	*IL1RL1*		Huvec	HCM
rs3771175	rs13408661	0.99	2	102321514	A	G	0.144	Intron	*IL1RL1*		Huvec	HCM
rs3771175	rs10173081	0.99	2	102323780	T	C	0.144	Intron	*IL1RL1*			5 cell types
rs3771175	rs3771175	1.00	2	102326642	A	T	0.146	UTR-3,intron	*IL1RL1*			HCM,NB4
rs3771175	rs10185897	0.89	2	102333222	A	C	0.134	Intron	*IL1RL1*			HFF-Myc,NB4
rs3771175	rs56179005	0.97	2	102340760	A	G	0.144	Near-gene	*IL18R1* (-4.8kb)	GM12878		GM06990,GM12878, Th1
rs3771175	rs72823669	0.97	2	102348465	T	G	0.144	Intron	*IL18R1*		GM12878	
rs3771175	rs72823677	0.93	2	102363483	T	C	0.147	Intron	*IL18R1*			HAEpiC
rs9865818	rs9842232	0.88	3	189562857	G	C	0.436	Intron	*LPP*		Huvec	PANC-1
rs9865818	rs9864554	0.86	3	189567376	T	G	0.429	Intron	*LPP*		Huvec	
rs9865818	rs9851967	0.87	3	189570322	T	C	0.434	Intron	*LPP*		Huvec	Gliobla,HRGEC,WI-38
rs9865818	rs11715549	0.87	3	189570812	G	C	0.434	Intron	*LPP*			8 cell types
rs9865818	rs11709294	0.85	3	189580729	A	T	0.429	Intron	*LPP*		HepG2	
rs9865818	rs2030516	0.85	3	189584433	T	C	0.429	Intron	*LPP*			HRCEpiC,HRE,RPTEC
rs9865818	rs4686955	0.85	3	189589073	G	A	0.429	Intron	*LPP*		HMEC, NHEK	
rs9865818	rs56046601	0.85	3	189591336	C	G	0.429	Intron	*LPP*		HMEC, NHEK	11 cell types
rs9865818	rs60946162	0.83	3	189616030	T	C	0.437	Intron	*LPP*			HA-h,HCFaa,

												HMVEC-dLy-Ad
rs17454584	rs45610037	0.98	4	123622458	A	G	0.244	Near-gene	*IL2* (-25.4kb)			11 cell types
rs17454584	rs59867199	0.74	4	123671681	T	C	0.299					HSMMtube
rs17454584	rs17389644	0.99	4	123717147	A	G	0.239	Near-gene	*IL21* (+36.1kb)			HMVEC-dLy-Neo
rs17616434	rs28393318	0.92	4	38460662	G	A	0.239	Intron	*TLR10*	GM12878		GM12864,GM12865, GM12878
rs17616434	rs10012017	0.92	4	38461028	T	G	0.239	Near-gene	*TLR10* (-22bp)			98 cell types
rs17616434	rs10034903	0.92	4	38461073	G	C	0.239	Near-gene	*TLR10* (-67bp)			96 cell types
rs17616434	rs10004195	0.91	4	38461119	A	T	0.242	Near-gene	*TLR10* (-113bp)			47 cell types
rs17616434	rs12233670	0.92	4	38463611	T	C	0.239	Near-gene	*TLR10* (-2.6kb)		GM12878	5 cell types
rs17616434	rs1135430	0.93	4	38465756	C	T	0.240	Near-gene	*TLR10* (-4.8kb)			6 cell types
rs17616434	rs11936050	0.93	4	38465919	T	C	0.240	Near-gene	*TLR10* (-4.9kb)		NHEK	5 cell types
rs17616434	rs4833093	0.93	4	38466135	T	G	0.240	Near-gene	*TLR10* (-5.1kb)		NHEK	A549
rs17616434	rs4833095	0.95	4	38476105	C	T	0.240	Missense	*TLR1*			HL-60
rs17616434	rs5743551	0.99	4	38484049	C	T	0.247	Near-gene	*TLR1* (-1.2kb)		GM12878, Huvec	22 cell types
rs17616434	rs9306967	0.90	4	38484306	C	G	0.226	Near-gene	*TLR1* (-1.5kb)		GM12878	
rs17616434	rs2013740	0.80	4	38568132	G	A	0.252	Intron	*FAM114A1*		5 cell types	
rs10056340	rs7735355	0.94	5	110181194	C	A	0.179			NHEK		24 cell types
rs10056340	rs7735519	0.94	5	110181240	A	C	0.179			NHEK, NHLF		33 cell types
rs10056340	rs3844182	0.80	5	110187493	C	T	0.214					HSMM,HSMMtube
rs10056340	rs7710963	0.99	5	110192528	C	T	0.180					HIPEpiC,Jurkat
rs10056340	rs7728612	0.99	5	110192573	T	C	0.180					HIPEpiC,Jurkat
rs10056340	rs12655815	0.80	5	110196417	A	G	0.214					GM12865
rs10056340	rs6594475	0.80	5	110198733	G	A	0.214					6 cell types
rs10056340	rs3851453	0.80	5	110204201	G	A	0.214				NHEK	HMEC,HSMMtube, Jurkat
rs10056340	rs7712464	0.80	5	110217055	T	C	0.214			HMEC	NHEK	32 cell types
rs10056340	rs10056340	1.00	5	110217951	G	T	0.181				NHEK	9 cell types
rs10056340	rs7734638	0.80	5	110221611	G	A	0.214					SKMC
rs10056340	rs4432941	0.80	5	110221630	T	G	0.214					HSMM,SKMC
rs10056340	rs4377748	0.80	5	110221668	G	A	0.214					HSMM,SKMC
rs10056340	rs7709594	0.80	5	110225324	A	T	0.214					SAEC
rs10056340	rs1423153	0.81	5	110229473	G	C	0.211					74 cell types
rs6906021	rs9273358	0.83	6	32733997	T	C	0.394	Near-gene	*HLA-DQB1* (+1.2kb)			GM12865
rs6906021	rs6906021	1.00	6	32734289	C	T	0.434	Near-gene	*HLA-DQB1* (930bp)		GM12878	GM12878
rs6932730	rs6932730	1.00	6	31462161	C	T	0.235	Near-gene	*MICA* (-17.2kb)			4 cell types
rs6932730	rs34821683	1.00	6	31469953	C	T	0.235	Near-gene	*MICA* (-9.4kb)			WERI-Rb-1
rs6932730	rs7739560	0.99	6	31472769	T	C	0.234	Near-gene	*MICA* (-6.6kb)	HepG2,	Huvec,	68 cell types

										K562	NHLF	
rs6932730	rs6930344	1.00	6	31475968	A	C	0.235	Near-gene	*MICA* (-3.4kb)	8 cell types		43 cell types
rs6932730	rs6937174	1.00	6	31477164	A	G	0.235	Near-gene	*MICA* (-2.2kb)	4 cell types	4 cell types	6 cell types
rs4410871	rs6470578	0.98	8	128878739	T	A	0.306			4 cell types	HMEC, Huvec	
rs4410871	rs4410871	1.00	8	128884211	T	C	0.306			HMEC	Huvec, NHEK	23 cell types
rs2155219	rs61893460	0.85	11	75968802	A	G	0.440	Near-gene	*C11orf30* (+28.6kb)		Huvec	
rs2155219	rs2155219	1.00	11	75976842	T	G	0.483	Near-gene	*C11orf30* (+36.6kb)		Huvec	Stellate
rs2155219	rs11236797	0.85	11	75977297	A	C	0.441	Near-gene	*C11orf30* (+37.1kb)		Huvec	47 cell types
rs1059513	rs1059513	1.00	12	55775976	C	T	0.105	UTR-3	*STAT6*		HMEC, NHEK	Hepatocytes,HMEC, HPDE6-E6E7

Supplementary Table 10. Coding variants in LD (r^2 > 0.8) with the top SNP in the 10 loci identified in the EAGLE sensitization GWAS

Top SNP	SNP in LD	r^2 with the top SNP	CHR	POS (hg18)	Minor Allele	Major Allele	MAF	Function	In Gene	Amino Acid change
rs17454584	rs1127348	1.00	4	123500310	C	T	0.2402	Synon	*KIAA1109*	
rs17616434	rs4833095	0.95	4	38476105	C	T	0.2402	Missense	*TLR1*	N>S
rs17616434	chr4:38798935	0.94	4	38475330	T	C	0.2402	Synon	*TLR1*	
rs6932730	rs1063630	0.83	6	31486337	G	T	0.2126	Missense	*MICA*	W>G
rs6932730	rs61738275	0.83	6	31488177	T	C	0.2126	Missense	*MICA*	P>L

Supplementary Table 11. Description of the 5q22.1 locus with respect to a) previous reports of disease association and b) linkage disequilibrium (1000 Genomes reference population)

a)

SNP	MAF	Risk allele	Literature GWAS			EAGLE atopy results	
			Phenotype	OR	References(s)	OR	*P* value
rs10056340 (index)	0.16	G	NA	NA	NA	1.30	5.00E-014
rs17513503	0.07	G	AR	1.28	1	1.26	3.24E-006
rs1837253	0.27	C	Asthma	1.17	2,3	1.05	0.1397
rs3806932	0.45	G	PEE	1.85	4	0.91	0.0001
rs1898671	0.35	T	AR	1.15	1	1.08	0.0038
rs2416257	0.15	A	EOS, Atopic Asthma	-6.1, 0.83	5	0.91	0.0116
rs1438673	0.50	T	Asthma	0.84	6	0.90	2.07E-005
rs6594499	0.49	C	Atopy	1.11	7	1.11	2.20E-005

(1) Ramasamy et al J Allergy Clin Immunol. 2011 Nov;128(5):996-1005

(2) Hirota et al. Nat Genet. 2011 Jul 31;43(9):893-6.

(3) Torgerson et al. Nat Genet. 2011 Jul 31;43(9):887-92.

(4) Rothenberg et al. Nat Genet. 2010 Apr;42(4):289-91

(5) Gudbjartsson et al. Nat Genet. 2009 Mar;41(3):342-7.

(6) Ferreira et al. Lancet. 2011 Sep 10;378(9795):1006-14.

(7) 23 & Me (replication study published in same issue of NG)

b)

Linkage disequilibrium (r^2)

	Atopy (EAGLE)	AR	Asthma	PEE	AR	EOS	Asthma	Atopy (23&Me)
	rs10056340	rs17513503	rs1837253	rs3806932	rs1898671	rs2416257	rs1438673	
rs10056340	1.00							
rs17513503	0.24	1.00						
rs1837253	0.00	0.00	1.00					
rs3806932	0.00	0.00	0.00	1.00				
rs1898671	0.00	0.00	0.14	**0.53**	1.00			
rs2416257	0.01	0.00	0.03	0.28	0.12	1.00		
rs1438673	0.00	0.01	0.03	**0.78**	0.06	0.22	1.00	
rs6594499	0.00	0.00	0.02	**0.77**	**0.56**	0.22	**0.98**	1.00

Supplementary Table 12. Gene set enrichment analysis (MAGENTA) results based on the discovery GWAS

Database	Gene Set	Gene set size	Nominal GSEA *P* value (95 percent. cutoff)	FDR (95 percent. cutoff)	Expected #genes > 95 perc. cutoff	Observed #genes > 95 perc. cutoff
KEGG	KEGG_AUTOIMMUNE_THYROID_DISEASE	32	9.9e-07	**2e-04**	2	10
KEGG	KEGG_ALLOGRAFT_REJECTION	27	9.9e-07	**2e-04**	1	10
KEGG	KEGG_ASTHMA	20	3.4e-05	**3e-04**	1	7
BIOCARTA	TH1TH2_PATHWAY	18	1.7e-05	**0.0011**	1	7
Ingenuity	PTEN.Signaling	24	2e-04	**0.0017**	1	7
Ingenuity	Fc.Epsilon.RI.Signaling	17	0.000108	**0.0022**	1	6
BIOCARTA	ASBCELL_PATHWAY	11	1e-04	**0.0023**	1	5
Ingenuity	Neuregulin.Signaling	26	1e-04	**0.0025333**	1	7
KEGG	KEGG_GRAFT_VERSUS_HOST_DISEASE	29	4e-04	**0.006975**	1	7
Ingenuity	Ephrin.Receptor.Signaling	36	3e-04	**0.007175**	2	8
Ingenuity	IGF-1.Signaling	18	0.0012	**0.00864**	1	5
BIOCARTA	IL4_PATHWAY	10	0.001	0.0152	1	4
KEGG	KEGG_TYPE_I_DIABETES_MELLITUS	33	9e-04	0.01636	2	7
Ingenuity	Calcium.Signaling	10	0.0126	0.0244556	1	3
Ingenuity	IL-4.Signaling	16	0.0067	0.0245875	1	4
Ingenuity	ERK.MAPK.Signaling	24	0.0061	0.02482	1	5
Ingenuity	VEGF.Signaling	16	0.0069	0.0270167	1	4
Ingenuity	Ceramide.Signaling	16	0.0081	0.0272571	1	4
Ingenuity	Insulin.Receptor.Signaling	34	0.0064	0.0306	2	6
KEGG	KEGG_INTESTINAL_IMMUNE_NETWORK_FOR_IGA_PRODUCTION	39	0.0024	0.0340143	2	7
KEGG	KEGG_HEMATOPOIETIC_CELL_LINEAGE	76	0.0014	0.0355	4	11
Ingenuity	GM-CSF.Signaling	20	0.0153	0.03765	1	4
Ingenuity	IL-6.Signaling	28	0.0127	0.0387462	1	5
Ingenuity	Integrin.Signaling	38	0.0133	0.0402333	2	6
Ingenuity	G-Protein.Coupled.Receptor.Signaling	19	0.0157	0.0407083	1	4
BIOCARTA	NKT_PATHWAY	25	8e-04	0.0418	1	6
Ingenuity	PDGF.Signaling	21	0.0206	0.0449688	1	4
KEGG	KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION	190	6e-04	0.0460375	10	20
KEGG	KEGG_ONE_CARBON_POOL_BY_FOLATE	17	0.0087	0.0495111	1	4
Ingenuity	B.Cell.Receptor.Signaling	33	0.021	0.0575235	2	5
Ingenuity	LXR.RXR.Activation	35	0.0276	0.0655611	2	5
Ingenuity	Neurotrophin.TRK.Signaling	16	0.0425	0.072985	1	3
Ingenuity	IL-2.Signaling	16	0.0432	0.0749421	1	3
KEGG	KEGG_JAK_STAT_SIGNALING_PATHWAY	117	0.0039	0.0817455	6	13
KEGG	KEGG_VIRAL_MYOCARDITIS	57	0.0072	0.08533	3	8

Supplementary Table 13. Detailed description of the 11 most significant gene sets (FDR < 0.01) from the gene set enrichment (MAGENTA) analysis

Database	Gene_Set	Gene	Gene *P* value	Effect	SNP	SNP *P* value	Symptom (23andMe) replication *P* value / consistent direction of effect
KEGG	KEGG_AUTOIMMUNE_THYROID_DISEASE	*HLA-DQA1*	4.207502E-09	-0.1471	rs6906021	1.284e-08	Top-locus
KEGG	KEGG_AUTOIMMUNE_THYROID_DISEASE	*HLA-DRB1*	5.231583E-09	-0.1471	rs6906021	1.284e-08	Top-locus
KEGG	KEGG_AUTOIMMUNE_THYROID_DISEASE	*IL2*	1.900989E-05	-0.1287	rs17454584	9.468e-06	Top-locus
KEGG	KEGG_AUTOIMMUNE_THYROID_DISEASE	*HLA-DQB1*	6.043204E-05	-0.1471	rs6906021	1.284e-08	Top-locus
KEGG	KEGG_AUTOIMMUNE_THYROID_DISEASE	*HLA-DQA2*	1.578755E-04	-0.1471	rs6906021	1.284e-08	Top-locus
KEGG	KEGG_AUTOIMMUNE_THYROID_DISEASE	*IL5*	6.092586E-04	0.1258	rs17622991	6.576e-05	**0.004/yes**
KEGG	KEGG_AUTOIMMUNE_THYROID_DISEASE	*IL4*	9.084372E-04	0.1521	rs734244	5.518e-05	0.14/yes
KEGG	KEGG_AUTOIMMUNE_THYROID_DISEASE	*HLA-DRB5*	1.536889E-03	0.114	rs9272535	8.364e-05	Top-locus
KEGG	KEGG_AUTOIMMUNE_THYROID_DISEASE	*HLA-B*	2.059049E-03	0.1633	rs6932730	7.944e-07	Top-locus
KEGG	KEGG_AUTOIMMUNE_THYROID_DISEASE	*FASLG*	3.988489E-03	-0.1324	rs1159378	0.00014	0.56/NA
KEGG	KEGG_AUTOIMMUNE_THYROID_DISEASE	*CD86*	1.129385E-02	0.12	rs1920291	0.000252	**0.01/yes**
KEGG	KEGG_AUTOIMMUNE_THYROID_DISEASE	*CD40*	1.161140E-02	-0.1156	rs12624433	0.0001557	0.28/yes
KEGG	KEGG_AUTOIMMUNE_THYROID_DISEASE	*TG*	4.224887E-02	-0.112	rs988068	0.0001416	0.94/NA
Non-significant genes	*HLA-DOB, HLA-DRA, IFNA13, IFNA2, IFNA1, IFNA6, HLA-C, IFNA8, CGA, HLA-DMB, HLA-DMA, IFNA14, IFNA17, CD80, IFNA16, IFNA7, IFNA10, CD28, IFNA21, PRF1, IFNA4, CTLA4, TSHB, HLA-DPA1, HLA-DOA, HLA-DPB1, TSHR, FAS, HLA-A, GZMB, TPO, HLA-F, HLA-E, IL10, IFNA5, HLA-G*						
KEGG	KEGG_ALLOGRAFT_REJECTION	*HLA-DQA1*	4.207502E-09	-0.1471	rs6906021	1.284e-08	Top-locus
KEGG	KEGG_ALLOGRAFT_REJECTION	*HLA-DRB1*	5.231583E-09	-0.1471	rs6906021	1.284e-08	Top-locus
KEGG	KEGG_ALLOGRAFT_REJECTION	*IL2*	1.900989E-05	-0.1287	rs17454584	9.468e-06	Top-locus
KEGG	KEGG_ALLOGRAFT_REJECTION	*HLA-DQB1*	6.043204E-05	-0.1471	rs6906021	1.284e-08	Top-locus
KEGG	KEGG_ALLOGRAFT_REJECTION	*HLA-DQA2*	1.578755E-04	-0.1471	rs6906021	1.284e-08	Top-locus
KEGG	KEGG_ALLOGRAFT_REJECTION	*IL5*	6.092586E-04	0.1258	rs17622991	6.576e-05	**0.004/yes**
KEGG	KEGG_ALLOGRAFT_REJECTION	*IL4*	9.084372E-04	0.1521	rs734244	5.518e-05	0.14/yes
KEGG	KEGG_ALLOGRAFT_REJECTION	*HLA-DRB5*	1.536889E-03	0.114	rs9272535	8.364e-05	Top-locus
KEGG	KEGG_ALLOGRAFT_REJECTION	*HLA-B*	2.059049E-03	0.1633	rs6932730	7.944e-07	Top-locus
KEGG	KEGG_ALLOGRAFT_REJECTION	*TNF*	3.972224E-03	-0.1748	rs4947324	9.074e-06	Top-locus
KEGG	KEGG_ALLOGRAFT_REJECTION	*FASLG*	3.988489E-03	-0.1324	rs1159378	0.00014	0.56/NA
KEGG	KEGG_ALLOGRAFT_REJECTION	*CD86*	1.129385E-02	0.12	rs1920291	0.000252	**0.01/yes**
KEGG	KEGG_ALLOGRAFT_REJECTION	*CD40*	1.161140E-02	-0.1156	rs12624433	0.0001557	0.28/yes
Non-significant genes	*IL12A, HLA-DOB, HLA-DRA, HLA-C, HLA-DMB, HLA-DMA, IFNG, CD80, CD28, PRF1, HLA-DPA1, HLA-DOA, HLA-DPB1, FAS, HLA-A, GZMB, HLA-F HLA-E, IL10, IL12B, HLA-G*						
KEGG	KEGG_ASTHMA	*HLA-DQA1*	4.207502E-09	-0.1471	rs6906021	1.284e-08	Top-locus
KEGG	KEGG_ASTHMA	*HLA-DRB1*	5.231583E-09	-0.1471	rs6906021	1.284e-08	Top-locus
KEGG	KEGG_ASTHMA	*HLA-DQB1*	6.043204E-05	-0.1471	rs6906021	1.284e-08	Top-locus
KEGG	KEGG_ASTHMA	*HLA-DQA2*	1.578755E-04	-0.1471	rs6906021	1.284e-08	Top-locus
KEGG	KEGG_ASTHMA	*IL5*	6.092586E-04	0.1258	rs17622991	6.576e-05	**0.004/yes**
KEGG	KEGG_ASTHMA	*IL13*	6.799815E-04	0.1521	rs734244	5.518e-05	0.14/yes
KEGG	KEGG_ASTHMA	*IL4*	9.084372E-04	0.1521	rs734244	5.518e-05	0.14/yes
KEGG	KEGG_ASTHMA	*HLA-DRB5*	1.536889E-03	0.114	rs9272535	8.364e-05	Top-locus
KEGG	KEGG_ASTHMA	*TNF*	3.972224E-03	-0.1748	rs4947324	9.074e-06	Top-locus
KEGG	KEGG_ASTHMA	*FCER1A*	9.093377E-03	0.2436	rs12140357	0.0002424	0.07/yes
KEGG	KEGG_ASTHMA	*CD40*	1.161140E-02	-0.1156	rs12624433	0.0001557	0.28/yes
Non-significant genes	*HLA-DOB, HLA-DRA, HLA-DMB, RNASE3, HLA-DMA, FCER1G, CCL11, EPX, HLA-DPA1, HLA-DOA, HLA-DPB1, PRG2, IL3, MS4A2, IL10, IL9*						

BIOCARTA	TH1TH2_PATHWAY	*HLA-DRB1*	5.231583E-09	-0.1471	rs6906021	1.284e-08	Top-locus
BIOCARTA	TH1TH2_PATHWAY	*IL2*	1.900989E-05	-0.1287	rs17454584	9.468e-06	Top-locus
BIOCARTA	TH1TH2_PATHWAY	*IL18R1*	5.490214E-04	0.1122	rs6759479	8.267e-06	Top-locus
BIOCARTA	TH1TH2_PATHWAY	*IL4*	9.084372E-04	0.1521	rs734244	5.518e-05	0.14/yes
BIOCARTA	TH1TH2_PATHWAY	*IL4R*	5.072796E-03	-0.1529	rs2234898	0.0001067	0.17/yes
BIOCARTA	TH1TH2_PATHWAY	*CD86*	1.129385E-02	0.12	rs1920291	0.000252	**0.01/yes**
BIOCARTA	TH1TH2_PATHWAY	*CD40*	1.161140E-02	-0.1156	rs12624433	0.0001557	0.28/yes
Non-significant genes	*IL12A, HLA-DRA, IL2RA, IFNG, CD28, IFNGR2, IL18, IFNGR1, IL12RB2, IL12RB1, IL12B*						
Ingenuity	PTEN.Signaling	*FASLG*	3.988489E-03	-0.1324	rs1159378	0.00014	0.56/NA
Ingenuity	PTEN.Signaling	*BAD*	4.047106E-03	0.0942	rs10897487	0.000247	0.11/yes
Ingenuity	PTEN.Signaling	*CCND1*	1.275392E-02	-0.119	rs7109260	0.0002272	Missing
Ingenuity	PTEN.Signaling	*SHC1*	2.192242E-02	0.1072	rs12023499	0.0006063	0.33/yes
Ingenuity	PTEN.Signaling	*PTK2*	2.364044E-02	-0.098	rs10108278	0.0002812	0.72/NA
Ingenuity	PTEN.Signaling	*PTEN*	2.517105E-02	0.1088	rs10887758	0.000602	0.09/yes
Ingenuity	PTEN.Signaling	*PRKCZ*	2.546894E-02	-0.1007	rs3107156	0.0006142	**0.047/yes**
Non-significant genes	*BCAR1, PIK3R5, CASP3, PIK3CG, BCL2L11, BCL2, CDKN1B, RAF1, PDPK1, CBL, CASP9, ILK, YWHAH, BCL2L1, CDKN1A, LOC643751, GRB2*						
Ingenuity	Fc.Epsilon.RI.Signaling	*IL5*	6.092586E-04	0.1258	rs17622991	6.576e-05	**0.004/yes**
Ingenuity	Fc.Epsilon.RI.Signaling	*IL13*	6.799815E-04	0.1521	rs734244	5.518e-05	**0.03/yes**
Ingenuity	Fc.Epsilon.RI.Signaling	*IL4*	9.084372E-04	0.1521	rs734244	5.518e-05	0.14/yes
Ingenuity	Fc.Epsilon.RI.Signaling	*TNF*	3.972224E-03	-0.1748	rs4947324	9.074e-06	Top-locus
Ingenuity	Fc.Epsilon.RI.Signaling	*FCER1A*	9.093377E-03	0.2436	rs12140357	0.0002424	0.23/yes
Ingenuity	Fc.Epsilon.RI.Signaling	*PTPN11*	1.247699E-02	-0.0891	rs11066320	0.0005513	**0.01/yes**
Ingenuity	Fc.Epsilon.RI.Signaling	*FYN*	1.388087E-02	-0.1684	rs9487769	9.728e-05	0.47/no
Non-significant genes	*LYN, FCER1G, RAF1, LCP2, PDPK1, SYK, IL3, CSF2, GRAP2, LAT, MS4A2, GRB2*						
BIOCARTA	ASBCELL_PATHWAY	*HLA-DRB1*	5.231583E-09	-0.1471	rs6906021	1.284e-08	Top-locus
BIOCARTA	ASBCELL_PATHWAY	*IL2*	1.900989E-05	-0.1287	rs17454584	9.468e-06	Top-locus
BIOCARTA	ASBCELL_PATHWAY	*IL4*	9.084372E-04	0.1521	rs734244	5.518e-05	0.14/yes
BIOCARTA	ASBCELL_PATHWAY	*FASLG*	3.988489E-03	-0.1324	rs1159378	0.00014	Top-locus
BIOCARTA	ASBCELL_PATHWAY	*CD40*	1.161140E-02	-0.1156	rs12624433	0.0001557	0.28/yes
Non-significant genes	*HLA-DRA, CD4, CD80, CD28, FAS, IL10*						
Ingenuity	Neuregulin.Signaling	*MYC*	5.705052E-05	-0.1246	rs4326353	4.374e-06	Top-locus
Ingenuity	Neuregulin.Signaling	*ERBB3*	3.321814E-04	0.1068	rs2271189	4.938e-05	0.79/NA
Ingenuity	Neuregulin.Signaling	*BAD*	4.047106E-03	0.0942	rs10897487	0.000247	0.10/yes
Ingenuity	Neuregulin.Signaling	*PTPN11*	1.247699E-02	-0.0891	rs11066320	0.0005513	**0.01/yes**
Ingenuity	Neuregulin.Signaling	*SHC1*	2.192242E-02	0.1072	rs12023499	0.0006063	0.33/yes
Ingenuity	Neuregulin.Signaling	*PTEN*	2.517105E-02	0.1088	rs10887758	0.000602	0.09/yes
Ingenuity	Neuregulin.Signaling	*GRB7*	3.400819E-02	-0.1122	rs2313430	0.001369	Missing
Non-significant genes	*RNF41, MATK, EGFR, CDK5, ADAM17, PICK1, CDKN1B, CDK5R1, FRAP1, RAF1, ERBB2, PDPK1, RPS6, DLG4, GRB2, SRC, ERBB4, PSEN1, ERRFI1*						
KEGG	KEGG_GRAFT_VERSUS_HOST_DISEASE	*HLA-DQA1*	4.207502E-09	-0.1471	rs6906021	1.284e-08	Top-locus
KEGG	KEGG_GRAFT_VERSUS_HOST_DISEASE	*HLA-DRB1*	5.231583E-09	-0.1471	rs6906021	1.284e-08	Top-locus
KEGG	KEGG_GRAFT_VERSUS_HOST_DISEASE	*IL2*	1.900989E-05	-0.1287	rs17454584	9.468e-06	Top-locus
KEGG	KEGG_GRAFT_VERSUS_HOST_DISEASE	*HLA-DQB1*	6.043204E-05	-0.1471	rs6906021	1.284e-08	Top-locus

KEGG	KEGG_GRAFT_VERSUS_HOST_DISEASE	*HLA-DQA2*	1.578755E-04	-0.1471	rs6906021	1.284e-08	Top-locus
KEGG	KEGG_GRAFT_VERSUS_HOST_DISEASE	*HLA-DRB5*	1.536889E-03	0.114	rs9272535	8.364e-05	Top-locus
KEGG	KEGG_GRAFT_VERSUS_HOST_DISEASE	*HLA-B*	2.059049E-03	0.1633	rs6932730	7.944e-07	Top-locus
KEGG	KEGG_GRAFT_VERSUS_HOST_DISEASE	*TNF*	3.972224E-03	-0.1748	rs4947324	9.074e-06	Top-locus
KEGG	KEGG_GRAFT_VERSUS_HOST_DISEASE	*FASLG*	3.988489E-03	-0.1324	rs1159378	0.00014	0.56/NA
KEGG	KEGG_GRAFT_VERSUS_HOST_DISEASE	*CD86*	1.129385E-02	0.12	rs1920291	0.000252	**0.01/yes**
Non-significant genes	*HLA-DOB, KIR2DL1, IL1B, KIR2DL3, HLA-DRA, KLRC1, KIR3DL2, HLA-C, HLA-DMB, HLA-DMA, IFNG, IL1A, CD80, CD28, PRF1, HLA-DPA1, HLA-DOA, KLRD1, HLA-DPB1, FAS, HLA-A, IL6, GZMB, HLA-F, HLA-E, KIR3DL1, HLA-G*						
Ingenuity	Ephrin.Receptor.Signaling	*SH2D3C*	4.616593E-03	-0.1053	rs7865146	0.0001473	Missing
Ingenuity	Ephrin.Receptor.Signaling	*ARHGEF15*	8.832307E-03	-0.1071	rs4792722	0.0002665	0.40/yes
Ingenuity	Ephrin.Receptor.Signaling	*PTPN11*	1.247699E-02	-0.0891	rs11066320	0.0005513	**5.5 E-04/yes**
Ingenuity	Ephrin.Receptor.Signaling	*FYN*	1.388087E-02	-0.1684	rs9487769	9.728e-05	0.90/NA
Ingenuity	Ephrin.Receptor.Signaling	*ACP1*	2.003080E-02	-0.1373	rs385272	0.0003645	0.81/NA
Ingenuity	Ephrin.Receptor.Signaling	*PXN*	2.172863E-02	0.153	rs11611311	0.000642	0.70/NA
Ingenuity	Ephrin.Receptor.Signaling	*SHC1*	2.192242E-02	0.1072	rs12023499	0.0006063	0.33/yes
Ingenuity	Ephrin.Receptor.Signaling	*PTK2*	2.364044E-02	-0.098	rs10108278	0.0002812	0.72/NA
Non-significant genes	*JAK2, BCAR1, ITSN1, SDC2, KALRN, SORBS1, DOK1, SDCBP, STAT3, FGF1, RAF1, NCK2, NGEF, ADAM10, EGF, ABI1, ABL1, RAPGEF1, PTPN13, AXIN1, RHOA, ANGPT1, CXCR4, RASA1, LOC643751, GRB2, SRC, CXCL12*						
Ingenuity	IGF-1.Signaling	*BAD*	4.047106E-03	0.0942	rs10897487	0.000247	0.11/yes
Ingenuity	IGF-1.Signaling	*PTPN11*	1.247699E-02	-0.0891	rs11066320	0.0005513	**5.5 E-04/yes**
Ingenuity	IGF-1.Signaling	*PXN*	2.172863E-02	0.153	rs11611311	0.000642	0.70/NA
Ingenuity	IGF-1.Signaling	*SHC1*	2.192242E-02	0.1072	rs12023499	0.0006063	0.33/yes
Ingenuity	IGF-1.Signaling	*PTK2*	2.364044E-02	-0.098	rs10108278	0.0002812	0.72/NA
Non-significant genes	*GRB10, IGF1R, FOS, SRF, RAF1, IGF1, NEDD4, PDPK1, CASP9, JUN, MAPK8, RASA1, GRB2*						

Supplementary Table 14. Replication of sensitization top SNPs (current meta-analysis) in a previous large-scale genome wide association study of asthma. Moffat MF, Gut IG, Demenais F, et al. A large-scale consortium-based genomewide association study of asthma. N Engl J Med 2010;125:328-35.

				Sensitization results from current meta-analysis					Asthma results			
Position	**Gene**	**SNP**	**Effect allele**	**OR (95% CI)**	***P* value**	**proxy**	**Dist**	**R2/Dprime**	**Proxy effect allele**	**OR (95% CI)**	***P* value**	**Same direction of effect**
11	*C11orf30*	rs2155219	T	1.18 (1.13, 1.22)	1.4E-18	rs7130588	28511	0.74/1	G	1.10 (1.05-1.15)	**8.0E-05**	yes
12	*STAT6*	rs1059513	T	1.30 (1.21, 1.39)	1.0E-14	Identical	0	1/1	-	1.09 (1.02-1.16)	0.01	yes
5	*SLC25A46*	rs10056340	T	0.83 (0.78, 0.87)	5.2E-14	rs12659961	3048	1/1	T	0.92 (0.88-0.97)	**0.002**	yes
6	*HLADQB1*	rs6906021	T	0.87 (0.83, 0.90)	2.2E-12	rs2858312	40919	0.55/1	G	0.92 (0.88-0.96)	**2.9E-04***	yes
2	*IL1RL1/IL18R1*	rs3771175	A	0.83 (0.78, 0.88)	4.9E-11	rs13431828	5557	1/1	T	0.83 (0.77-0.89)	**2.0E-07***	yes
4	*TLR1/6/10*	rs17616434	T	1.23 (1.18, 1.29)	5.2E-11[+]	rs4833095	13166	0.96/1	T	1.07 (1.02-1.12)	0.006	yes
3	*LPP*	rs9865818	A	0.89 (0.86, 0.92)	2.7E-10	Identical	0	1/1	-	0.93 (0.88-0.97)	**0.001**	yes
8	*MYC*	rs4410871	T	1.14 (1.09, 1.19)	5.4E-10	Identical	0	1/1	-	1.02 (0.97-1.07)	0.50	yes
4	*IL2/ADAD1*	rs17454584	A	0.87 (0.83, 0.91)	5.5E-10	rs1127348	72572	1/1	T	0.94 (0.89-0.99)	0.01	yes
6	*HLA-B/MICA*	rs6932730	T	1.14 (1.09, 1.20)	4.2E-08	Identical	0	1/1	-	1.09 (1.04-1.15)	**0.001**	yes

P value in bold if significant after Bonferroni correction for the 10 loci tested ($P < 0.005$)

* Locus was genome-wide significant in both meta-analyses

[+] *P* value was calculated by random effects model due to evidence of heterogeneity between studies (Heterogeneity *P* for Cochrane's Q statistic < 0.05, $I^2 > 25\%$)

Supplementary Table 15. Replication of top loci from the sensitization analysis in a large-scale GWAS on eczema. Paternoster et al. Nat Genet 2012; 44: 187-92.

				Allergic sensitization Current meta-analysis		Eczema		
Region	**SNP**	**Nearest gene**	**Effect allele**	**OR (95% CI)**	***P* value**	**OR**	***P* value**	**Same direction of effect**
11q13.5	rs2155219	*C11orf30*	t	1.18 (1.13-1.22)	1.4E-18	1.08 (1.03-1.14)	**7.0E-04***	yes
12q13.3	rs1059513	*STAT6*	t	1.30 (1.21-1.39)	1.0E-14	1.14 (1.05-1.25)	**0.001***	yes
5q22.1	rs10056340	*SLC25A46*	t	0.83 (0.78-0.87)	5.2E-14	0.96 (0.90-1.02)	0.16	yes
6p21.32	rs6906021	*HLADQB1*	t	0.87 (0.83-0.90)	2.2E-12	0.97 (0.92-1.02)	0.18	yes
2q12.1	rs3771175	*IL1RL1/IL18R1*	a	0.83 (0.78-0.88)	4.9E-11	0.93 (0.86-1.01)	0.08	yes
4p14	rs17616434	*TLR1/6/10*	t	1.23 (1.18-1.29)	5.2E-11[+]	1.02 (0.97-1.08)	0.42	yes
3q28	rs9865818	*LPP*	a	0.89 (0.86-0.92)	2.7E-10	0.97 (0.92-1.02)	0.20	yes
8q24.21	rs4410871	*MYC/PVT1*	t	1.14 (1.09-1.19)	5.4E-10	1.02 (0.97-1.07)	0.44	yes
4q27	rs17454584	*IL2/ADAD1*	a	0.87 (0.83-0.91)	5.5E-10	0.93 (0.88-0.98)	0.01	yes
6p21.33	rs6932730	*HLA-B/MICA*	t	1.14 (1.09-1.20)	4.2E-08	1.00 (0.94-1.06)	0.96	NA

P value in bold if significant after Bonferroni correction for the 10 loci tested ($P < 0.005$)

* significantly associated after Bonferroni correction for the 10 genome-wide significant loci ($P < 0.005$)

[+] *P* value was calculated by random effects model due to evidence of heterogeneity between studies (Heterogeneity *P* for Cochrane's Q statistic < 0.05, $I^2 > 25\%$)

Supplementary Table 16. Sensitization association results from the current discovery meta-analysis for loci associated with sensitization to grass allergens, total IgE level or blood eosinophil level in previous GWAS

a) Grass sensitization

				Grass sensitization	Sensitization Current metaanalysis	
Position	**Gene**	**SNP**	**Effect allele**	***P* value**	**OR (95% CI)**	***P* value**
5q22.1	*TMEM232*	rs17513503	G	1.2E-08	1.26 (1.14-1.40)	**3.4E-06***
6p21.32	*HLA region*	rs7775228	C	1.6E-09	1.10 (1.02-1.18)	**0.011***
11q13.5	*C11ORF30*	rs2155219	T	9.4E-09	1.20 (1.14-1.27)	**1.8E-12***

* Locus was genome wide significant in both meta-analyses

P value is in bold if significant after Bonferroni correction for the 3 loci tested (*P* <0.016)

Reference: Ramasamy et al. J Allergy Clin immunol 2011; 128: 996-1005.

b) Total IgE

					Total IgE	Sensitization (current meta-analysis)	
Position	**Gene**	**Ref**	**SNP**	**Effect allele**	***P* value**	**OR (95% CI)**	***P* value**
1q23.2	*FCER1A*	1	rs2251746	C	4.5E-26	0.92 (0.87-0.97)	**0.002**
-	*FCER1A*	1	rs2494264	A	9.4E-20	0.95 (0.90-1.00)	0.04
-	*FCER1A*	1	rs4656784	G	1.7E-16	0.89 (0.84-0.95)	**2.7E-04**
5	*IL13*	1	rs20541	A	3.4E-18	1.12 (1.04-1.19)	**0.001**
-	*IL13*	1	rs2243297	A	1.5E-08	1.20 (1.03-1.40)	0.02
-	*RAD50*	2	rs2040704	G	4.5E-08	1.14 (1.07-1.21)	**6.9E-05**
6	*HLA-A*	1	rs2571391	C	1.2E-15	0.96 (0.91-1.02)	0.18
-	*HLA-A*	1	rs2517754	A	3.6E-09	1.09 (1.00-1.19)	0.05
-	*HLA-G*	1	rs2523809	T	4.3E-08	1.09 (1.00-1.18)	0.04
6p21.32	*HLA-DRB1*	3	rs9271300	C	8.3E-15	1.13 (1.04-1.23)	**0.004***
6	*HLA-DQA2*	1	rs2858331	G	1.4E-08	1.00 (0.94-1.06)	1.00
12	*STAT6*	1	rs1059513	C	2.0E-12	0.74 (0.68-0.82)	**1.6E-10***
-	*STAT6*	1	rs167769	T	4.0E-10	1.08 (1.02-1.14)	**0.008**

* Locus was genome wide significant in both meta-analyses

P value is in bold if significant after Bonferroni correction for the 6 loci tested (*P* <0.0083)

Reference no. 1: Granada et al. J Allergy Clin Immunol 2011

Reference no. 2: Weidinger et al. PloS Genetics 2008; 4: e100166.

Reference no. 3: Moffatt et al. N Eng J Med 2010; 363: 1211-21.

c) Eosinophil numbers

				Eosinophil numbers	Sensitization Current metaanalysis	
Position	**Gene**	**SNP**	**Effect allele**	***P* value**	**OR (95% CI)**	***P* value**
2q12	*IL1RL1*	rs1420101	T	5.3E-14	1.11 (1.05-1.16)	**9.8E-05***
2q13	*IKZF2*	rs12619285	G	5.4E-10	0.98 (0.92-1.03)	0.38
3q21	*GATA2*	rs4857855	T	8.6E-17	1.03 (0.97-1.10)	0.32
5q31	*IL5*	rs4143832	G	1.2E-10	0.98 (0.92-1.04)	0.45
12q24	*SH2B3*	rs3184504	T	6.5E-19	0.91 (0.86-0.96)	**1.6E-04**

* Locus was genome wide significant in both meta-analyses

P value is in bold if significant after Bonferroni correction for the 5 loci tested (*P* <0.01)

Reference: Gudbjartsson et al. Nat Genet 2009; 41: 342-7.

Supplementary Table 17. Sensitization association results from the current discovery meta-analysis for loci associated with allergic rhinitis, asthma or eczema in previous GWAS

a) Allergic rhinitis

				Grass sensitization	Sensitization Current metaanalysis	
Position	**Gene**	**SNP**	**Effect allele**	**P-value**	**OR (95% CI)**	***P* value**
11q13.5	*C11ORF30*	rs2155219	T	3.8E-08	1.20 (1.14-1.27)	**1.8E-12***

* Locus was genome wide significant in both meta-analyses

Reference: Ramasamy et al. J Allergy Clin immunol 2011; 128: 996-1005.

b) Asthma

					Asthma	Sensitization (current meta-analysis)	
Position	**Gene**	**Ref**	**SNP**	**Effect allele**	**P-value**	**OR (95% CI)**	***P* value**
1q21.3	*IL6R*	1	rs4129267	T	2.3E-08	1.08 (1.02-1.14)	0.01
1q31.3	*DENND1B*	2	rs2786098	T	9.3E-11	0.96 (0.90-1.02)	0.22
2q12.1	*IL1RL1*	3	rs3771180	T	1.5E-15	1.17 (1.09-1.25)	**2.1E-05***
-	*IL1RL1*	4	rs1420101	T	5.5E-12	1.11 (1.05-1.16)	**9.8E-05**
-	*IL18R1*	5	rs3771166	A	3.4E-09	0.89 (0.85-0.94)	**1.5E-05**
5	*PDE4D*	6	rs1588265	G	2.5E-08	1.00 (0.95-1.06)	0.97
5	*TSLP*	3	rs1837253	T	1.0E-14	1.05 (0.98-1.11)	0.14
6p21.3	*HLA-DQB1*	5	rs9273349	T	7.0E-14	0.93 (0.87-1:00)	0.04*
9p24.1	*IL33*	3	rs2381416	A	1.7E-12	1.02 (0.97-1.08)	0.43
-	*IL33*	5	rs1342326	C	9.2E-10	1.01 (0.94-1.08)	0.85
11q13.5	*C11ORF30*	1	rs7130588	G	1.8E-08	1.18 (1.12-1.25)	**3.7E-10***
15q22.3	*SMAD3*	5	rs744910	A	3.9E-09	0.95 (0.90-1.00)	0.03
17q12-21	*GSDM*	3	rs11078927	T	2.2E-16	1.04 (0.99-1.10)	0.12
-	*GSDM1*	5	rs3894194	A	4.6E-09	1.06 (1.01-1.11)	0.02
-	*GSDMB*	5	rs2305480	A	9.6E-08	0.96 (0.91-1.02)	0.16
22q12.3	*IL2RB*	5	rs2284033	A	1.1E-08	0.99 (0.94-1.04)	0.69

* Locus was genome wide significant in both meta-analyses

P value is in bold if significant after Bonferroni correction for the 11 loci tested (*P* <0.0045)

Reference no. 1: Ferreira et al. Lancet 2011; 378: 1006-14.
Reference no. 2: Sleiman et al. N Engl J Med 2010; 362: 36-44.
Reference no. 3: Torgerson at al. Nat Genet 2011; 43: 887-92.
Reference no. 4: Gudbjartsson et al. Nat Genet 2009; 41: 342-7.
Reference no. 5: Moffatt et al. N Eng J Med 2010; 363: 1211-21.
Reference no. 6: Himes et al. Am J Hum Gen 2009; 84: 581-93.

c) Eczema

					Eczema	Sensitization (current meta-analysis)	
Position	**Gene**	**Ref**	**SNP**	**Effect allele**	**P-value**	**OR (95% CI)**	***P* value**
1q21	*EDC-region/FLG*	1	rs6661961	T	1.2E-09	1.07 (1.02-1.13)	0.009
-	*EDC-region/FLG*	2	rs9050	A	1.9E-08	1.10 (0.97-1.25)	0.13
5	*KIF3A*	2	rs2897442	T	7.1E-09	0.91 (0.86-0.96)	**9.8E-04***
11	*OVOL1*	2	rs479844	A	1.1E-13	0.94 (0.89-0.99)	0.02
11q13.5	*C11ORF30*	1	rs7927894	T	7.6E-10	1.20 (1.14-1.27)	**1.0E-11***
19	*ACTL9*	2	rs2164983	A	7.1E-09	1.06 (0.96-1.17)	0.27

* Locus was genome wide significant in both meta-analyses

P value in bold if significant after Bonferroni correction for the 6 loci tested (*P* <0.008)

Ref no. 1: Esparza-Gordillo et al. Nat Genet 2009; 41: 596-601.

Ref no. 2: Paternoster et al. Nat Genet 2012; 44: 187-92.

Supplementary Table 18. Population attributable risk fraction (PARF) of the 10 top SNPs for sensitization and allergic rhinitis. Estimates were calculated from population based cohorts of children and adults

Phenotype	Cohort description	Age	Phenotype description	Cases/controls	**Comprehensive PARF (95% CI) [1]**	**Conservative PARF (95% CI) [2]**
Sensitization, specific IgE 0.35 IU/mL	HEALTH2006 replication	18-69y	Birch, grass, cat and house dust mite	739/2402	**0.71 (0.54,0.83)**	**0.35 (0.17,0.51)**
	B58C replication	44-45y	Cat, mixed grass and house dust mite	634/1498	**0.69 (0.48,0.82)**	**0.27 (0.06,0.44)**
Sensitization, specific IgE 3.5 IU/mL	HEALTH2006 replication	18-69y	Birch, grass, cat and house dust mite	466/2675	**0.80 (0.64,0.89)**	**0.33 (0.07,0.52)**
	B58C replication	44-45y	Cat, mixed grass and house dust mite	289/1843	**0.75 (0.47,0.89)**	**0.41 (0.07,0.63)**
Sensitization SPT 3mm	HEALTH2006 replication	18-69y	10 inhalant allergens	659/1502	**0.71 (0.51,0.83)**	**0.29 (0.09,0.46)**
	ALSPAC discovery+replication	7.5y	Grass, house dust mite, cat, egg, peanut, nuts	804/3181	**0.76 (0.58,0.87)**	**0.41 (0.23,0.55)**
Allergic rhinitis	HEALTH2006 replication	18-69y	Questionnaire, hayfever current	558/2527	**0.64 (0.40,0.79)**	**0.28 (0.04,0.46)**
	B58C replication	42y	Questionnaire, hayfever ever	529/1853	**0.73 (0.52,0.85)**	**0.48 (0.26,0.60)**
	ALSPAC discovery+replication	11y	Questionnaire, hayfever current	902/3773	**0.80 (0.67,0.89)**	**0.26 (0.08,0.41)**

1) The 'comprehensive´ PARF was calculated using the 10 SNP risk score as continuous variable and a hypothetical individual with no risk alleles as baseline.

2) The 'conservative' PARF was calculated using the lowest 10% risk score as baseline ('unexposed group')

Supplementary Table 19. GWAS Catalogue reports for SNPs correlated ($R^2 > 0.5$) with the top-SNP from the 10 sensitization loci

Allergic sensitization Current meta-analysis				Relationship		GWAS Cataloque				
Position	**Nearest Gene**	**Index SNP**	**Cataloque SNP *P* Value**	**Distance**	**Rsquare / D-prime**	**GWAS Cataloque SNP**	***P* Value**	**Disease or Trait**	**Same direction of effect**	**Reference**
2q12.1	*IL1RL1/IL18R1*	rs3771175	2.0E-05	6593	0.96/1	rs3771180	2.00E-15	Asthma	yes	Torgerson DG Nat Genet, 2011
4q27	*IL2/ADAD1*	rs17454584	5.4E-05	24070	0.65/1	rs17388568	3.00E-06	Type 1 diabetes	yes	WTCCC Nature, 2007
-	-	-	5.4E-05	24070	0.65/1	rs17388568	6.00E-06	Type 1 diabetes autoantibodies	yes	Plagnol V PLoS Genet, 2011
-	-	-	5.4E-05	24070	0.65/1	rs17388568	9.00E-07	Ulcerative colitis	yes	Anderson CA Nat Genet, 2011
6p21.33	*HLA-B/MICA*	rs6932730	5.7E-06	378	0.71/1	rs13437082	5.00E-08	Height	no	Soranzo N PLoS Genet, 2009
8q24.21	*MYC/PVT1*	rs4410871	1.8E-07	0	1.00/1	rs4410871	8.00E-09	Multiple sclerosis	no	Sawcer S Nature, 2011
11q13.5	*C11orf30*	rs2155219	1.6E-12	0	1.00/1	rs2155219	5.00E-16	Ulcerative colitis	yes	Anderson CA Nat Genet, 2011
-	-	-	1.6E-12	0	1.00/1	rs2155219	1.00E-08	IgE grass sensitization	yes	Ramasamy A J Allergy Clin Immunol, 2011
-	-	-	1.6E-12	0	1.00/1	rs2155219	4.00E-08	Allergic rhinitis	yes	Ramasamy A J Allergy Clin Immunol, 2011
-	-	-	9.2E-12	2122	0.69/1	rs7927894	1.00E-09	Crohn's disease	yes	Barrett JC Nat Genet , 2008
-	-	-	9.2E-12	2122	0.69/1	rs7927894	8.00E-10	Atopic dermatitis	yes	Esparza-Gordillo J Nat Genet, 2009
-	-	-	3.3E-10	28511	0.66/1	rs7130588	2.00E-08	Asthma	yes	Ferreira MA Lancet , 2011
12q13.3	*STAT6*	rs1059513	1.4E-10	0	1.00/1	rs1059513	2.00E-12	IgE levels	yes	Granada M J Allergy Clin Immunol, 2011

For each of the 10 genome-wide significant SNPs in the sensitization meta-analysis, all snps within a +/- 500 kb distance and with an r^2 above 0.5 were identified. Matching SNPs earlier reported in a GWAS were identified in the GWAS catalogue.

Supplementary Note

Supplementary results

Detailed description of the 10 genome wide significant loci

The chr11q13.5 locus, represented in our study by rs2155219, has previously been associated with allergic sensitization,[2] allergic rhinitis,[2] asthma,[3] eczema,[4] ulcerative colitis[5] and Crohn's disease[6] (r2 > 0.66 for all leading SNPs and with same direction of effect). Rs2155219 is located between *C11orf30* and *LRRC32*. The risk allele (T) is strongly associated with reduced expression levels of *C11orf30* in white blood cells and adipose tissue and less strongly with reduced levels of *LRRC32* in white blood cells **(Supplementary Table 6)**. At present, the potential immunological function is unknown for both genes. However, the association with multiple atopic and immune-related diseases suggests this to be a central locus for immune regulation.

We confirmed *STAT6*, a key-regulator of the Th2 immune response, as an important atopy gene. The top SNP was previously genome-wide significantly associated with Total IgE levels.[7, 8] The risk (T) allele was associated with increased expression of *STAT6* in EBV-transformed lymphocytes, white blood cells and whole blood **(Supplementary Table 6)**.

rs10056340 is located on chromosome 5q22.1, near six variants previously reported to associate with eosinophil counts and atopic asthma (rs2416257)[9], pediatric eosinophilic esophagitis (rs3806932)[10], asthma (rs1837253[11, 12], rs1438673[3]) and allergic rhinitis (rs17513503 and rs1898671)[2]. Interestingly, in individuals of European ancestry (1000 Genomes Project Consortium, 2010), the atopy variant rs10056340 is in low LD with all six variants (r^2 < 0.05 for all, except rs17513503, r^2 = 0.24), suggesting that it represents a new risk variant for allergic disease in this region. Furthermore, analysis of LD between the six nearby SNPs previously reported in the literature suggests that they too are largely independent of each other, with the exception of rs3806932, rs1898671 and rs1438673, which may tag the same underlying causal variant (**Supplementary Table 11**). Therefore, together with our results, these data suggest that at least five independent variants in this region contribute to a broad range of allergic phenotypes. Four genes are located within 250 kb of rs10056340, namely *SLC25A46*, *TSLP*, *WDR36* and *CAMK4*, of which rs10056340 was associated with expression of *CAMK4* in lymphoblastoid cell lines (LCLs) **(Supplementary Table 6)**. *TSLP* is a plausible causal candidate, given its role in promoting Th2 cell responses.[13]

Varation in human leukocyte antigen (HLA) haplotypes was first linked to ragweed sensitization forty years ago[14] and the major histocompatibility complex (MHC) region became established as a genetic determinant of allergy and asthma well before the era of molecular genetics.[15] Recognition of the role of HLA class II molecules in regulating the immune response, particularly through allergen presentation, made them strong biological candidate genes for allergic diseases.[16] By the start of the GWAS era, *HLA-DQ* and *HLA-DR* were among the most widely reported genetic associations for asthma and allergy.[17] Our strongest signal in this region (rs6906021) was also top-SNP in the accompanying paper on self-reported allergy.[1] It is located in the *HLA-DQ* region and is strongly associated with expression of *HLA-DQA1* and *HLA-DQB1* and to a lesser extent *HLA-DRB* in white blood cells, lymphocytes and whole blood **(Supplementary Table 6)**. This SNP is in complete LD (D'=1) with the top SNP for grass pollen sensitization reported by Ramasamy and colleagues

(rs7775228) although the two SNPs are poorly correlated (r^2=0.16), suggesting that there may be distinct genetic signals at this locus influencing aeroallergen sensitization in general, and grass pollen sensitization more specifically. Rs6906021 is in almost complete LD and moderately correlated with the top SNP for asthma in the GABRIEL meta-analysis[18] (rs9273349: D'=0.98, r^2=0.54). This raises the possibility that the association of *HLA-DQB1* with asthma, reported in the GABRIEL study is wholly or partially explained by an association with allergic sensitization, despite no association at this locus with circulating total IgE. In common with a recent GWAS meta-analysis of grass pollen sensitization in adults,[2] we found that sensitization to aeroallergens was associated with the *HLA-DQB1* locus, and not the *HLA-DRB1* locus. This demonstrates that there are independent HLA-related effects on total IgE and aeroallergen sensitization.

We identified another genome-wide significant locus, 6p21.33, in the MHC-complex near *HLA-B* and *MIC-A*. The top-SNP (rs6932730) was associated with expression of several MHC molecules, including *HLA-C* and *MIC-B* **(Supplementary Table 6)**. This locus has not previously been genome-wide significantly associated with sensitization or atopic disease. However, the region has previously been associated with other immune-related diseases including, crohn's disease, [19] drug hypersensitivity, [20] and psoriasis.[21]

The locus on chromosome 2q tagging *IL1RL1/IL18R1/IL18RAP* is strongly supported by this meta-analysis and the accompanying paper on self-reported allergy.[1] *IL1RL1* encodes a receptor for IL33 involved in Th2 signalling and is located on several cell types, including mast cells, T-helper (Th) 2 cells, innate type 2 helper cells or nuocytes, and epithelial cells. It also encodes a soluble form (IL1RL1-a) that may inhibit IL33 signaling. The genes encoding IL18R and IL18RAP form the alpha and beta chain of IL-18R, which regulates Th-1 cells. The most strongly associated SNP rs3771175 is in full LD with SNPs previously found in two GWAS performed on asthma,[3, 12] and in much lower LD with SNPs found in the largest GWAS on asthma to date.[18] That GWAS identified a haplotype that extends from *IL1RL1* to *IL18R1* and encodes several non synonymous amino acid changes in the intracellular domain of *IL1RL1* that may be involved in downstream signaling. Rs3771175 is in moderate LD with a coding SNP in exon 3 of *IL1RL1* (rs1041973), which was associated with asthma and soluble IL1RL1-a levels in blood in a Dutch population.[22] The SNP was associated with expression of *IL18RAP* in white blood cells and whole blood **(Supplementary Table 6)** and with expression of *IL1R1* in B-cells **(Supplementary Table 7)**. LD with rs1420101, a SNP previously reported to be associated with blood eosinophils and asthma is low.[9]

The chromosome 4 top-SNP rs17616434 is located between *Toll-like receptor 6* (*TLR6) and Toll-like receptor 1 (TLR1)* and is in linkage disequilibrium ($r^2 > 0.8$) with 5 genes: *TLR1, 6,* - and *10, MIR574* and *FAM114A1*. *TLR 1 ,6,* and *-10* encode family members of pattern recognition molecules expressed on the cell surface and involved in innate immunity. The immune system may mature through contact with microbial compounds mediated by Toll like receptors, and this interaction is thought to confer protection against allergy development.[23] Rs17616434 tags a haplotype that has previously been associated with asthma and atopy.[24-26] TLR dependent gene expression and cytokine production was altered in individuals with risk variants suggesting that polymorphisms in this region modify specific T ell dependent cytokine expression after stimulation of their respective heterodimers.[26] *MIR574* encodes a micro RNA (MIR 574-5p) that has been reported to be differentially expressed in lung tissue from an ovalbumin induced asthma mouse model, yet human data are not available.[27] *FAM114A1* is a gene of unknown function.

rs9865818 is located on chromosome 3q28, in the second intron of the *LPP* gene, near a variant (rs1464510) recently reported to associate with generalized vitiligo (GV)[28], celiac disease (CD)[29] and

asthma.[3] The rs9865818:G allele that increases atopy risk is in phase (r^2 = 0.59) with the rs1464510:C allele that decreases the risk of GV (OR = 0.76) and CD (OR = 0.77), and increases the risk of asthma (OR = 1.08). Rs9865818 was associated with expression of *LPP* (a member of the LIM protein gene family) in B-cells but not in monocytes **(Supplementary Table 7)** suggesting that LPP may be the causal gene underlying association at this locus. *LPP* has a number of known functions including a role in cell migration and proliferation[30] and serves as a substrate of the protein-tyrosine phosphatase 1B, a regulator of signalling pathways linked to Ras signalling.[31] Also, association analyses of gene expression levels measured in monocytes[32] identified a nearby variant – rs9864529, which is in LD (r^2 = 0.73) with rs9865818 – that is a *cis* acting eQTL for *BCL6* ($P = 5.2x10^{-9}$), a gene located 618 kb away. *BCL6* encodes a zinc finger transcriptional repressor that is normally expressed in both B cells and $CD4^+$ T cells within germinal centers.[33-35] Mice deficient in BCL6 developed an inflammatory response in multiple organs characterized by infiltrations of eosinophils and IgE-bearing B lymphocytes typical of a Th2-mediated hyperimmune response.[36] Consistent with this observation, the rs9865818:G allele that increases atopy risk is in phase with rs9864529:G allele that decreases *BCL6* expression. It is therefore also possible that rs9864529 is associated with increased risk of allergic sensitization by down-regulation of *BCL6* expression, which in turn promotes a Th2-mediated immune response.

The chromosome 4q27 locus is situated in a region of moderate LD of 4 genes: *KIAA1109* (a gene of unknown function), *ADAD1* (adenosine deaminase domain containing 1 is a testis-specific expressed gene), and Interleukin *(IL)-2* and *IL21*. This region has been observed in multiple GWAS for inflammatory diseases, including Celiac disease[37], Lupus[38], Crohn's disease[39], Ulcerative Colitis[40] and rheumatoid arthritis.[41] However, LD of our top locus rs17454584 is moderate with the SNPs reported in those GWASes (max r2 = 0.586, D'= 1). *IL2* and *IL21* are strong candidate genes for atopy in this region. One of the functions of IL2 produced mainly by CD4+ and CD8 + T cells is its action as a B cell growth factor and stimulator of antibody synthesis, a.o. IgE. IL21 produced by T cells, NKT cells, and the Th17 subset of CD4+ T cells, regulates B cell function by affecting antibody isotype balance, proliferation, apoptosis and differentiation into plasma cells.[42] The top-SNP at this locus (rs17454584) was associated with expression of *IL2* in B-cells but not in monocytes **(Supplementary Table 7)** suggesting that LPP may be the causal gene underlying association at this locus. Previous candidate studies have suggested a role of SNPs in *IL2*[43] and *IL21*[44] in atopy and asthma. In the latter study, one SNP in *IL21* in moderate LD with the top hit from our GWAS, was associated with serum IL21 levels.

Population attributable risk fraction and individual risk

The 10 genome-wide significant SNPs had a high population attributable risk for sensitization and allergic rhinitis in both childhood and adult populations **(Supplementary Table 18).** Despite these high population attributable risks, the combined genetic risk score discriminated poorly between individuals with and without allergic sensitization. In B58C, genetic risk scores were below the median for the population for 43% of 1722 individuals with any detectable specific IgE, and for 40% of 769 persons with specific IgE >3.5kU/L. In Health2006, the corresponding percentages were identical (43% of 755 sensitized individuals and 40% of 477 with specific IgE>3.5kU/L), with 42% of 673 SPT-positive cases positioned below the median of the genetic risk score. Conversely, the top 20% of the genetic risk score distribution contributed only 25% of sensitized individuals and 25% of high spIgE levels in the B58C. Similarly, in Health2006, the top 20% of risk score identified 27% cases with detectable spIgE, 30% cases with high spIgE, and 28% of SPT-positive participants. This means that although the 10 most significant loci together explained (statistically) a high

proportion of allergic sensitization, the top SNPs in combination were of little value for discriminating individuals at risk of allergy. The population attributable risk fraction depends not only on the strength of association (measured here as the per-allele odds ratio) but also the prevalence of the risk factor (the risk allele frequency). Thus, common genetic variants associated with modestly increased relative risks of disease or pathophysiology can contribute substantially to the population burden, but they are poor indicators of individual risk and explain little of the familial clustering of disease. This apparent paradox has been discussed in greater detail elsewhere, in the context of asthma.[45] It is possible that allergic sensitization is influenced strongly by unmeasured rare variants, in linkage disequilibrium with common haplotypes (high D' but low r^2), as is the case for eczema in relation to filaggrin mutations.[46] Theoretically, such rare variants could account for the population attributable risk observed at one or more of the loci identified by our genome-wide meta-analysis. But it is more likely that much of the genetic risk of allergic sensitization, at least in populations of European ancestry, arises from weak effects of multiple common polymorphisms. Unfortunately, these will be of very limited value for clinical prediction or for targeting preventive or therapeutic measures at individuals on the basis of genetic risk.

Study sample description

Australian Asthma Genetics Consortium (AAGC) discovery cohort

As part of the AAGC, we performed a GWAS of asthma in 7,197 unrelated individuals of confirmed European ancestry ascertained from the Australian population as described in detail elsewhere [1]. Skin-prick test results were available for 2,719 of these, including 1,871 who had a positive test to at least one common allergen (cases) and 848 who did not (controls). These individuals participated in one of six studies: QIMR (N=505), CAPS (N=49), LIWA (N=638), MESCA (N=141), TAHS (N=364) or Busselton (N=1,022). Genotyping was performed with Illumina 610K or 370K arrays and stringent quality control filters applied as described in [3]. Imputation to HapMap 3 (all 11 populations, Feb 2009 release) and 1000 Genomes Project (CEU, Mar 2010 release) SNPs was performed with Impute2 and SNPs tested for association with disease status using a Cochran-Mantel-Haenszel test with three strata representing three imputation analysis groups. Written informed consent was obtained from all study participants; parental written informed consent was obtained for participants under 18 years of age. This work was approved by the relevant ethics committees of the QIMR, University of Melbourne, Monash University and University of Western Australia.

AAGC replication cohort

As part of the AAGC, we genotyped 23 SNPs in a further 2,222 individuals with self-reported European ancestry from the Australian population. Of these, 1,210 had a positive skin-prick test to at least one common allergen (cases) whereas 1,012 did not (controls). These individuals participated in one of five studies: QIMR (N=205), COPD (N=665), LIWA (N=311), MNCA (N=428) or TAHS (N=613). Using data from the 23 SNPs and an additional 52 SNPs genotyped on these samples for other projects, we confirmed that none of the 2,222 individuals had been included in the AAGC discovery cohort. Genotyping was performed using the Sequenom MASSarray platform and SNPs tested for association with atopy status using a Cochran-Mantel-Haenszel test with five strata representing the five individual cohorts. Written informed consent was obtained from all study participants; parental written informed consent was obtained for participants

under 18 years of age. This work was approved by the relevant ethics committees of the QIMR, University of Melbourne, Monash University and University of Western Australia.

The Avon Longitudinal Study of Parents and Children (ALSPAC)

The Avon Longitudinal Study of Parents and their Children (ALSPAC) is a longitudinal population-based birth cohort that recruited pregnant women residing in Avon, UK, with an expected delivery data between 1st April 1991 and 31st December 1992. 14,541 pregnant women were initially enrolled with 14,062 children born (see [47] and website http://www.alspac.bris.ac.uk). Biological samples including DNA have been collected for 10,121 of the children from this cohort. Ethical approval was obtained from the ALSPAC Law and Ethics committee and relevant local ethics committees, and written informed consent provided by all parents in both the discovery and replication studies. The atopic status of the children was determined at 7–8 years of age by skin prick test response to a panel of up to 12 common allergens including house dust mite, grass pollen, cat, egg, peanut and mixed nuts. A positive response was defined as a mean weal diameter of >3 mm with an absent response to negative control solution, and atopy was defined as a positive response to one or more of house dust mite, grass pollen, cat, egg, peanut and mixed nuts.

Discovery Cohort Genotyping and Statistical Analysis

Genotyping was carried out at two different centres (The Wellcome Trust Sanger Centre, Cambridge, UK and Laboratory Corporation of America, Burlington, NC, US) using the Illumina HumanHap 550 array (Illumina, Inc., San Diego, CA). Individuals were excluded on the basis of the following: sex mismatches, minimal or excessive heterozygosity, disproportionate levels of individual missingness (>3%), cryptic relatedness measured as proportion of identity by descent (IBD > 0.1), and insufficient sample replication (IBD < 0.8). The remaining individuals were assessed for evidence of population stratification by multidimensional scaling analysis and compared with Hapmap II (release 22) European descent (CEU), Han Chinese, Japanese and Yoruba reference populations; all individuals with non-European ancestry were removed. SNPs with a minor allele frequency of < 1%, a call rate of < 95% or evidence for violations of Hardy-Weinberg equilibrium ($P < 5*10^{-7}$) were removed. Autosomal genotypic data were subsequently imputed using Markov Chain Haplotyping software (MACH v.1.0.16, Li et al. 2010) and phased haplotype data from CEU individuals (Hapmap release 22, Phase II NCBI B36, dbSNP 126) based on a cleaned dataset of 8,365 individuals and 464,311 autosomal SNPs. After imputation, all SNPs with indication of poor imputation quality ($r^{\wedge 2}<0.30$) were removed. The final imputed dataset consisted of 8,005 subjects each with 2,483,534 imputed markers, 3,512 of which also had SPT phenotype information (743 cases and 2,771 controls).

Genome-wide association analysis of SPT was carried out in MACH2DAT[48, 49] regressing expected allelic dosage on case-control status.

ALSPAC Replication Cohort Genotyping and Statistical Analysis

Subjects were genotyped using the Illumina HumanHap550 quad genome-wide SNP genotyping platform by 23andMe subcontracting the Wellcome Trust Sanger Institute, Cambridge, UK and the Laboratory Corporation of America, Burlington, NC, US. Individuals were excluded on the basis of having incorrect gender assignments; minimal or excessive heterozygosity (<0.32 and >0.345 for the Sanger data and <0.31 and >0.33 for the LabCorp data); disproportionate levels of individual missingness (>3%); evidence of

cryptic relatedness (>10% IBD) and being of non-European ancestry. The resulting dataset consisted of 9233 individuals. SNPs with a minor allele frequency of < 1% and call rate of < 95% were removed. Furthermore, only SNPs which passed an exact test of Hardy-Weinberg equilibrium ($P > 5*10^{-7}$) were considered for analysis. Genotypes were subsequently imputed with MACH 1.0.16 Markov Chain Haplotyping software, using CEPH individuals from phase 2 of the HapMap project as a reference set (release 22). Of the 9233 ALSPAC genotyped individuals, 8005 were unrelated Caucasian and of these 3718 also had SPT phenotype information, 512 cases and 1523 controls were included in the discovery analysis and 292 cases and 1391 controls were included in the ALSPAC replication set.

Replication association analysis of the 10 SNPs was carried out as per the discovery cohort methods.

British 1958 birth cohort (B58C)

At the age of 44-45 years, the cohort were followed up with a biomedical examination and blood sampling,[50] from which a DNA collection was established as a nationally representative reference panel (http://www.b58cgene.sgul.ac.uk/). All protocols, information sheets and consent forms for the B58C fieldwork were approved by the UK SouthEast Multi-Centre Research Ethics Committee in August 2002. Details are available online at http://www.b58cgene.sgul.ac.uk/consent.php. The discovery phase of the analysis used two non-overlapping subsets of the DNA collection which were selected as controls for use by the Wellcome Trust Case-Control Consortium (WTCCC)[51] and the Type 1 Diabetes Genetics Consortium (T1DGC).[52] Genotyping by the WTCCC used the Affymetrix 500K array and the T1DGC used the Illumina 550K array. Imputations using the HapMap 2 (release 21) template were performed using SNPTEST for the WTCCC subset and MACH for the T1DGC subset. Within-cohort logistic regression analyses for AD were performed using Quicktest for the WTCCC subset and ProbAbel for the T1DGC subset.

In silico replication analyses were performed using Illumina 550K/610K genotypes deposited by the GABRIEL consortium[18] and by the WTCCC on cohort members that had not been included in the discovery sets. Imputations for the replication set using the HapMap 2 (release 21) template were performed using MACH and within-cohort logistic regression analyses for eczema were performed using ProbAbel.

CHOP

CHOP patients and controls were recruited at the Children's Hospital of Philadelphia between 2006 and 2010. All subjects were of self-reported Caucasian origin and resident in the Greater Philadelphia area. Ethical approval for this study was obtained from the Institutional Revue Board of the Children's Hospital of Philadelphia. Informed consent was obtained from the parents, and assent was obtained from the children. The study included 393 cases and 181 controls. Sensitization was defined by a positive Skin Prick test (>= 3mm) against panels of environmental allergens (Alternaria tenuis; Hormodendrum cladospor.; Birch (Betula spp.); Oak (Quercus spp.); Ragweed (Ambrosia spp.); Grass mix; Timothy (Phleum); Alternaria tenuis; Hormodendrum cladospor.; Mold Mix; Birch (Betula spp.); Oak (Quercus spp.); Tree mix; Hickory (Carya); Maple (Acer, Red); Ragweed (Ambrosia spp.); Weed mix) and Food (Milk, Cow; Turkey; Barley; Corn; Oat; Rice; Egg; Apple; Soybean; Almond; Black Walnut; Brazil nut; Cashew; Pistachio; Pecan; Hazelnut; Walnut; Peanut; Wheat; White Potato; Carrot; Greenbean; Peas, Beef; Chicken; Oyster; Scallops; Shrimp; Catfish; Cod; Flounder; Mackerel; Lake Trout; Salmon; Tuna; Whitefish; Clam; Crab Mix; Lobster). All CHOP samples were genotyped on either the Illumina HH550 or HH610 BeadChips (Illumina, San Diego) at the Center for Applied Genomics.

In addition to self-reported ancestry, Principal Component Analysis was carried on all cases and controls using smartPCA to reduce the risk of population stratification. Mean age of the case cohort was 9 years and 51% were males and 49% females.

Genotyping QC measures, imputation, analysis

Prior to imputation, quality control was carried out in *plink* resulting in the exclusion of 10,930 SNPs with call rates <95%, 22,252 SNPs with a minor allele frequency (MAF) <1% and 13,181 SNPs with Hardy Weinberg equilibrium $P<10^{-5}$; the genomic inflation factor (GIF) was 1.05. Imputation was carried out using Impute version 1, and the HapMap release 22 haplotypes as a reference. Statistical analysis was carried out using SNPTEST, assuming an additive model and taking genotype uncertainty into account.

COPSAC

The COPSAC birth cohort study is a prospective clinical study of a birth cohort of 411 infants born to mothers with a history of asthma. The newborns were enrolled at the age of 1 month, the recruitment of which was previously described in detail.[53-55] The study was approved by the Ethics Committee for Copenhagen (KF 01-289/96) and The Danish Data Protection Agency (2008-41-1754) and informed consent was obtained from both parents. Parents' sensitization status was used in the current study in order to optimize power (Largest number of sensitized individuals). Specific IgE antibody levels were determined via the ImmunoCAP assay [56] (Phadia AB, Uppsala, Sweden). Samples positive for the Phadiatop screening test (>= 0.35 IU/mL) were further analyzed for specific IgE against single allergens (*D. pteronyssinus*, cat dander, dog dander, horse dander, birch, timothy, mugwort and cladosporium).

High throughput genome-wide SNP genotyping were performed using the Illumina Infinium™ II HumanHap550 v1, v3 or quad BeadChip platform (Illumina, San Diego), at the Children's Hospital of Philadelphia's Center for Applied Genomics, as described previously.[57]

Statistical analysis was carried out using SNPTEST, assuming an additive model and taking genotype uncertainty into account.

Croatian Asthma Genetics Study (CAGS)

Recruitment for this case-control study was carried out in the Department of Paediatrics, Josip Bencevic General Hospital, Slavonski Brod, Croatia between 2006 and 2008. The setting is the catchment area of the hospital, comprising ~789 square miles of the Brodsko-Posavska County, Croatia - a stable mixed urban-rural population of Caucasian ancestry (total population ~160,000). The study was approved by the local ethics committee "Ethics committee of General Hospital "Dr Josip Bencevic" Slavonski Brod and Ethics committee of Medical Faculty, University of Zagreb, Croatia". Informed consent was obtained from all parents (and children when appropriate). Children with asthma aged 6 to 18 years (cases) were recruited into the study from the paediatric asthma clinic if the following criteria were met: (1) physician-diagnosed asthma, (2) asthma symptoms (wheeze, cough, or both) within the previous 12 months, and (3) current use of antiasthma medication. Children of the same age without respiratory symptoms (confirmed by an interviewer-administered questionnaire; controls) were randomly selected from patients with non-respiratory conditions attending the other hospital departments (e.g. fracture clinic); social and environmental variables matched with general population. Cases and controls were not matched by gender and age. Atopic sensitization was ascertained by skin prick testing (*Dermatophagoides pteronyssinus*, cat

dander, dog dander, birch, ragweed, mixed grass, egg, peanut; Stallergens S.A., Antony, France). We defined sensitization as a mean weal diameter 3 mm greater than negative control to at least one of the allergens tested.

deCODE

Icelanders of both sexes born 1910-1990 who attended an outpatient clinics of asthma and allergy specialists at the National University Hospital of Iceland and the Iceland Medical Center (Laeknasetrid) during the years 1977 to 2009 were recruited to the study. Atopy status was determined by assessing skin-prick test reactivity (SPT positive: wheal size > 3 mm or >50% of the histamine control) to 12 common aeroallergens: Betula, Timotej, Cladosporium, Alternaria, Cat, Dog, Horse, rumex crispus, rumex acetocella, dermatophagoides farinae and pteronyssinus and Dandelion (Greer Laboratories, Lenoir, NC, USA). 953 SPT positive atopy patients (all with asthma) and 297 SPT negative (wheal size < =1 mm) controls (259 with asthma) were included in the analysis. All participants provided informed consent and donated blood samples at the Patient Recruitment Center (Iceland). The study was approved by the National Bioethics Committee of Iceland and the Icelandic Data Protection Authority.

Genotyping was performed at deCODE genetics with Illumina HumanHap 300K or 370K Bead arrays. Imputation was performed using IMPUTE2 with the 1000 genomes August 2010 freeze as a reference. Prior to imputation, individuals with < 98% yield and SNPs with < 95% yield, minor allele frequency < 1% or Hardy-Weinberg equilibrium $P < 1 \times 10^{-6}$ were removed. *P* values have been adjusted for relatedness using a genomic control adjustment factors of 1.05. Case control association analysis was performed using SNP Test .

The Danish Glostrup Cohort (Health2006)

Between June 2006 and May 2008, a cross-sectional study was performed in the general population in Copenhagen, the Capital of Denmark. A random sample of 7931 subjects aged 18–69 years old was obtained from the Danish Central Personal Register, Ministry of Internal Affairs. All were Danish adults with Danish citizenship and born in Denmark. A total of 3471 (44%) subjects participated in a general health examination and 3329 (95.9%) responded to a questionnaire about atopic diseases. The participation rate was higher among older age-groups than among younger age groups in both genders.[58] The Ethical Committee of Copenhagen County approved the study (KA-20060011). A written informed consent form was obtained from all participants prior to the beginning of the study.

All serum samples were analyzed for serum specific IgE to birch, grass, cat, and house dust mite (Dermatophagoides pteronyssinus)) by using the ADVIA Centaur® assay (Siemens, Deerfield, Ill.,US). Skin prick test reactivity against a panel of 10 inhalant allergens was performed on 2,393 consecutive participants by using the Solu-prick (ALK-Abelló A/S, Hørsholm, Denmark).

Genotyping of SNPs was performed by the PCR KASPar genotyping system (KBiosciences, Hoddesdon, UK). Lowest call rate for SNPs was 0.98.

Data analyses were performed using the Statistical Products and Service Solutions package (SPSS Inc., Chicago, IL, U.S.A.) for Windows (release 15.0).

KORA

KORA (Cooperative Heath Research in the Region of Augsburg) exists since 1996 in the region of Augsburg in the southwest of Germany, and builds on the MONICA (Monitoring of trends and determinants in cardiovascular disease) project initiated in 1984.[59] KORA is a regional research platform for population-based surveys and a cohort of more than 18,000 subjects are actively followed up to date. Four cross-sectional health surveys have been performed in five-year intervals, each containing independent random samples of residents in the city of Augsburg and the two adjacent counties in the age-range between 25 to 74 years at baseline examination. The study followed the recommendations of the Declaration of Helsinki and was approved by the local ethical committees and Informed consent was given by all participants.

RNA was isolated from whole blood using PAXgene Blood miRNA Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions and quantified by NanoDrop 1000 Spectrophotometer (Thermo Fisher Scientific, DE, USA). Purity and integrity of the RNA was analyzed using the Agilent Bioanalyzer with the 6000 Nano LabChip reagent set (Agilent Technologies, Germany). Samples with low quality were excluded after manually inspection. Using the Illumina TotalPrep-96 RNA Amp Kit (Ambion), 500ng of RNA was reverse transcribed into cRNA, and biotin-UTP-labeled. 3000ng of cRNA were hybridized to the Illumina HumanHT-12 v3 Expression BeadChips, followed by washing steps as described in the Illumina protocol. The Illumina GenomeStudio V 2010.1 Gene Expression Module was used to impute missing values and for quality control. In detail, samples with less than 6,000 significantly detected probes ($P < 0.01$) were excluded (n=4). Subsequently, the probe level data were exported to the R environment for further processing. Quantile normalization and log2 transformation was performed in R using the lumi package from the Bioconductor open source software (http://www.bioconductor.org). Based on expression patterns of probes localized on the X and Y chromosome, respectively, samples which did not match the recorded sex were excluded. After quality control, expression data were available for 993 samples.

LISA/GINI

The influence of Life-style factors on the development of the Immune System and Allergies in East and West Germany PLUS the influence of traffic emissions and genetics (LISAplus) Study is a population based birth cohort study. A total of 3097 healthy, fullterm neonates were recruited between 1997 and 1999 in Munich, Leipzig, Wesel and Bad Honnef. The participants were not pre-selected based on family history of allergic diseases.[60]

A total of 5991 mothers and their newborns were recruited into the German Infant study on the influence of Nutrition Intervention PLUS environmental and genetic influences on allergy development (GINIplus) between September 1995 and June 1998 in Munich and Wesel. Infants with at least one allergic parent and/or sibling were allocated to the interventional study arm investigating the effect of different hydrolysed formulas for allergy prevention in the first year of life.[61] All children without a family history of allergic diseases and children whose parents did not give consent for the intervention were allocated to the non-interventional arm. Detailed descriptions of the LISAplus and GINIplus studies have been published elsewhere [62] and [63], respectively.

Blood for DNA and IgE measurement was collected at the age 6 and 10 years. For both studies, approval by the local Ethics Committees (Bavarian Board of Physicians, University of Leipzig, Board of Physicians of North-Rhine-Westphalia) and written consent from participant's families were obtained.

Allergic sensitization was defined by specific serum IgE concentrations, which were assayed by the CAP-RAST FEIA system (Pharmacia Diagnostics, Freiburg, Germany) according to the manufacturer's instructions. Screening tests were used for testing allergic sensitization against food allergens (fx5: egg, cow milk, wheat, peanut, soybean, and codfish) and inhalant allergens (sx1: *Dermatophagoides pteronyssinus*, cat, dog, rye, timothy grass, *Cladosporium herbarum*, birch, mugwort). The limit of detection for specific IgE was 0.35 IU/mL. Children were assigned as IgE positive, if their IgE values exceeded 3.5 IU/mL. Children with IgE levels did not exceed the detection limit were assigned as IgE negative.

In the discovery analysis, 333 children from the LISAplus study Munich with specifc IgE measurement available at 6 years of age were included. DNA was analysed using the Affymetrix Human SNP Array 5.0 for each individual. Genome-wide data was called using BRLMM-P algorithm and imputed in IMPUTE.[64]

Genome-wide association analysis of allergic sensitization was carried out in SNPTEST V1 (https://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html) regressing expected allelic dosage on case-control status.

For replication, 438 children from both studies with specifc IgE measurement at 6 or 10 years of age were included (321 (73%) children from the GINIplus study Munich and 117 (27%) children from the LISAplus study Munich)). 387 individuals (321 from the GINIplus study and 66 from the LISAplus study) were analysed using the Affymetrix Human SNP Array 5.0 and 51 individuals from the LISAplus study were analysed using Affymetrix Human SNP Array 6.0. Genotypes were called using BRLMM-P algorithm (5.0), respectively BIRDSEED V2 algorithm (6.0), imputed in IMPUTE2[22] and genome-wide association analysis of allergic sensitization was carried out in SNPTEST V2 (https://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html) regressing expected allelic dosage on case-control status.

Manchester Asthma and Allergy Study (MAAS)

The Manchester Asthma and Allergy Study is an unselected (i.a. population-based), birth cohort study.[65-69] The setting is the maternity catchment area of Wythenshawe and Stepping Hill Hospitals, comprising of 50 square miles of South Manchester and Cheshire, UK, a stable mixed urban-rural population. Study was approved by the Local Research Ethics Committee (South Manchester local research ethics committee: reference number: 03/SM/400). The study is registered as ISRCTN72673620 (www.controlled-trials.com/isrctn/pf/72673620).Informed consent was obtained from all parents and assent from the children when appropriate.

Screening & Recruitment

All pregnant women were screened for eligibility at antenatal visits (8th-10th week of pregnancy). The study was explained to the parents, and informed consent for initial questionnaires and skin prick testing was obtained. Both parents completed a questionnaire about their and their partner's history of asthma and allergic diseases and smoking habits. If the pregnant woman's partner was not present at the antenatal clinic visit, an invitation was sent for him to attend an open-access evening clinic for skin prick testing and questionnaire. Once both parents had completed questionnaires and skin prick testing, a full explanation of the proposed future follow-up for the child was given. Of the 1499 couples who met the inclusion criteria (<10 weeks of pregnancy, maternal age >18 years, questionnaire and skin test data available for both

parents), 288 declined to take part in the study. A total of 1185 participants had at least some evaluable data.

Follow-up

The children have been followed prospectively, and attended review clinics at ages 1, 3, 5, 8 and 11 years.

Sensitization

Atopic sensitization was ascertained by skin prick testing at age 1, 3, 5, 8 and 11 years (*D pteronyssinus*, cat, dog, grasses, moulds, milk, egg [Bayer, Elkahrt, IN, USA]). We also measured specific serum IgE to mite, cat, dog, grasses, milk, egg and peanut by ImmunoCAP^{TM} (Phadia, Uppsala, Sweden) is serum samples collected at ages 3, 5 and 8 years. The detection limit of the assay was 0.2 kUA/L. We used data from age 8 and age 11 years follow-ups for this study.

Genotyping

DNA samples were genotyping on an illumina 610 quad chip. The illumina genotypes were called using the Illumina GenCall application following the manufacturer's instructions. Quality control criteria for samples included: 97% call rate, exclusion of samples with an outlier autosomal heterozygosity (scree-plot visualisation) gender validation and sequenome genotype concordance. Quality control criteria for SNPs included a 95% call rate, HWE > $5.9x10^{-7}$, minor allele frequency > 0.005. Genotypes were imputated with IMPUTE version 2.1.2 with 1000 genomes and hapmap phase 3 reference genotypes. Association analysis was carried out using SNPTEST version 2.1 using frequentist with the score method.

Northern Finland Birth Cohort 1986 (NFBC1986)

The Northern Finland Birth Cohort 1986 comprises 9432 live-born children with an expected date of birth between July 1, 1985, and June 30, 1986 from the two northernmost provinces of Finland, Oulu and Lapland. The cohort covers over 99% of all the deliveries in the target area during that time (N=9,362 mothers with N=9,432 liveborn children).[70] At the age of 16, the cohort members were sent a postal questionnaire, and 80% returned it. At the same time, they were invited to a clinical examination with 74% taking part in it. DNA was extracted from blood samples given at the clinical examination for 6,266 subjects.

Sensitivity to cat, birch, timothy grass, and to house dust mite (Dermatophagoidespteronyssinus) was assessed by skin prick tests, together with histaminedihydrochloride (10 mg/ml) and diluent of the allergen extracts used as positive and negative controls. Skin reactions to the allergens were recorded after 15 minutes, taking the average of the maximum weal diameter and the diameter perpendicular to the maximum.[71]

Association analysis was conducted using plink. Informed consent for the use of the data including DNA was obtained from all subjects at the age of 16 years. The study was approved by ethics committees in Oulu (Finland) university in accordance with the Declaration of Helsinki.

Northern Finland Birth Cohort 1966 (NFBC1966)

The Northern Finland Birth Cohort 1966 comprises 12058 live-born children with an expected date of birth in 1966 from the two northernmost provinces of Finland, Oulu and Lapland. The cohort covers over 96% of all the deliveries in the target area during that time (N=12055 mothers with 12058 live-born children)

(Rantakallio P. Groups at risk in low birth weight infants and perinatal mortality.[72] At the age of 31 years, the cohort members living in the original target area or in the capital area were invited to a clinical examination, to which 71% (N=6033) participated.[73]

Sensitivity to cat, birch, timothy grass, and to house dust mite (Dermatophagoidespteronyssinus) was assessed by skin prick tests, together with histaminedihydrochloride (10 mg/ml) and diluent of theallergen extracts used as positive and negativecontrols. Skin reactions to the allergens wererecorded after 15 minutes, taking the average ofthe maximum weal diameter and the diameterperpendicular to the maximum.[74]

At the same time point,blood samples were drawn, and DNA was extracted successfully for 5753 participants. Genome-wide genotyping was performed with Illumina HumanCNV370DUO Analysis Beadchip platform at the Broad Institute, USA. Imputation of non-typed autosomal SNPs was performed with IMPUTE version 0.1.3 using the HapMap Phase II panel of phased haplotypes for CEU samples (release 21), NCBI build 35 as a reference panel. The association analyses were performed using SNPTEST.The Ethics Committees of the University of Oulu and Northern Ostrobothnia Hospital District approved the study and informed consent was obtained from all parents (or children where appropriate)

PIAMA

PIAMA is a birth cohort study consisting of two parts: a placebo controlled intervention study in which the effect of mite impermeable mattress covers was studied and a natural history study in which no intervention took place. Details of the study design have been published previously. Recruitment took place in 1996-1997. A screening questionnaire was distributed to pregnant women visiting one of 52 prenatal clinics at three regions in the Netherlands. A total of 10,232 pregnant women completed a validated screening questionnaire. Mothers reporting a history of asthma, current hay fever or allergy to pets or house dust mite were defined as allergic. Based on this screening, 7862 women were invited to participate, of whom 4,146 women (1327 allergic and 2819 nonallergic) gave written informed consent. The response rates to the annual questionnaires ranged from 3030 (92%) at age 1 to 2732 (83%) at age 8 years. DNA was collected from 2162 children at age 4 and/or 8 years. Genome-wide genotyping was performed within the framework of the Gabriel Consortium. For this study, DNA samples from 213 children with parental reported doctor diagnosed asthma ever at age 8 years and from 213 controls without doctor diagnosed asthma or wheeze ever at age 8 years were provided. From these children, 50 cases (≥ 1 skin test positive) and 176 controls were selected. Specific allergens tested for were Dermatophagoides pteronyssinus, Dermatophagoides farinae, Alternaria alternata, mixed grass pollen, mixed tree pollen, cat, and dog. Skin test positivity was defined as one or ore positive skin test with a diameter of 3 mm of larger. For specific IgE to inhalant allergens, we included 161 cases (≥ 0.35 IU/ml) and 176 controls. We tested by Radio Allergo Sorbent Test for any of the following allergens: Dermatophagoides pteronyssinus, Fel d1, Can f1, Dactylis Glomerata, Betula verrucosa, Alternaria Alternata, milk and egg. Controls were defined as children without specific IgE (<0.35 Iu/ml) to these allergens.

Genotyping was performed with an Illumina Human610 quad array. SNPs were excluded that fullfilled one or more of the following criteria: p-value for test of Hardy-Weinberg equilibrium $\leq$ 1E -7, genotyping call rate <95% or MAF < 1%. SNPs were imputed with IMPUTE version 2 software using HAPMAP CEU release #22 b36. Genome-wide association analyses were performed using SNPTEST version 1.1.5. The Medical Ethical Committees of the participating institutes approved the study.

Western Australian Pregnancy (Raine) cohort

Recruitment of the Western Australian Pregnancy (Raine) cohort has previously been described in detail.[75-77] In brief, between 1989 and 1991 2,900 pregnant women were recruited prior to 18-weeks gestation into a randomised controlled trial to evaluate the effects of repeated ultrasound in pregnancy. Recruitment predominantly took place at King Edward Memorial Hospital (Perth, Western Australia). Women were randomised to repeat ultrasound measurements at 18, 24, 28, 34 and 38 weeks gestation or to a regular ultrasound assessment at 18-weeks. Children have been comprehensively phenotyped from birth to 20 years of age (average ages of one, two, three, six, eight, ten, 14, 17 and currently 20) by trained members the Raine research team. Data collection included questionnaires completed by the child's primary carer and by the adolescent from age 14, physical assessments by trained assessors at all follow up years, DNA collection from the year 14 follow-up. Information on ever having AD diagnosed by a paediatrician or GP was collected using a questionnaire at 6 and 8 years of age. The study was conducted with appropriate institutional ethics approval from the King Edward Memorial Hospital and Princess Margaret Hospital for Children ethics boards, and written informed consent was obtained from all mothers and the children from age 18-years. The cohort has been shown to be representative of the population presenting to the antenatal tertiary referral centre in Western Australia.[78] Genotyping was performed using the Illumina 660w quad array and imputation of HapMap 2 (CEU release 22) SNPs was performed using MACH. Association testing was performed using MACH2DAT.

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14) Busselton Population Medical Research Foundation, Sir Charles Gairdner Hospital, Perth, WA, Australia.

EAGLE - the EArly Genetics & Lifecourse Epidemiology (EAGLE) Consortium

The results from the atopic dermatitis (AD) genome-wide association study were provided by the AD working group of the EArly Genetics & Lifecourse Epidemiology (EAGLE) Consortium. This group is coordinated by Lavinia Paternoster[1] & David Evans[1] and Marie Standl[2] & Joachim Heinrich[2]. The GWAS results in which we carried out the look-up are described in their paper, Paternoster et al. 2011. Meta-analysis of genome-wide association studies identifies three new risk loci for atopic dermatitis.Nat Genet 44(2):187-92.

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B-cells and monocyte eQTL study

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