

# Supplementary information

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

Klaus Bønnelykke; Melanie C Matheson; Tune H Pers; Raquel Granell; David P Strachan; Alexessander Couto Alves; Allan Linneberg; John A Curtin; Nicole M Warrington; Marie Standl; Marjan Kerkhoff; Ingileif Jonsdottir; Blazenka Kljaic Bukvic; Marika Kaakinen; Patrick Sleimann; Gudmar Thorleifsson; Unnur Thorsteinsdottir; Katharina Schramm; Svetlana Baltic; Eskil Kreiner-Møller; Angela Simpson; Beate St Pourcain; Lachlan Coin; Jennie Hui; Eugene H Walters; Carla M T Tiesler; David L Duffy; Graham Jones; AAGC; Susan M Ring; Wendy L McArdle; Loren Price; Colin F Robertson; Juha Pekkanen; Clara S Tang; Elisabeth Thiering; Grant W Montgomery; Anna-Liisa Hartikainen; Shyamali C Dharmage; Lise L Husemoen; Christian Herder; John P Kemp; Paul Elliot; Alan James; Melanie Waldenberger; Michael J Abramson; Benjamin P Fairfax; Julian C Knight; Ramneek Gupta; Philip J Thompson; Patrick Holt; Peter Sly; Joel N Hirschhorn; Mario Blekic; Stephan Weidinger; Hakon Hakonarsson; Kari Stefansson; Joachim Heinrich; Dirkje S Postma; Adnan Custovic; Craig E Pennell; Marjo-Riitta Jarvelin; Gerard H Koppelman; Nicholas Timpson; Manuel A Ferreira; Hans Bisgaard & John A Henderson for the EARly Genetics and Lifecourse Epidemiology (EAGLE) Consortium

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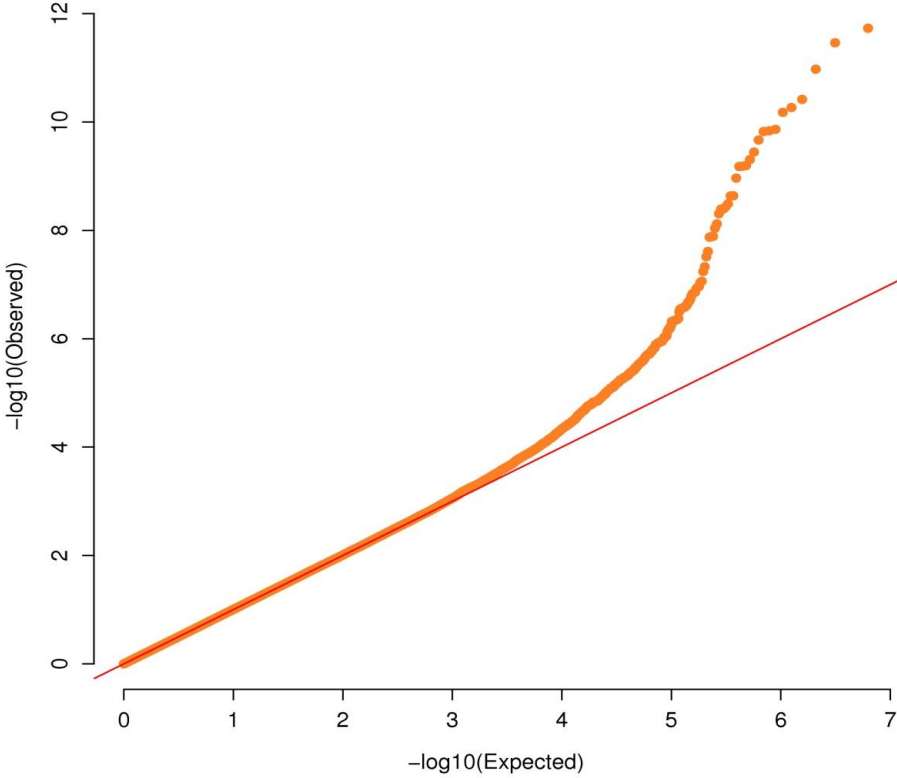
**Supplementary Figures (1-5)**

**Supplementary Tables (1-19)**

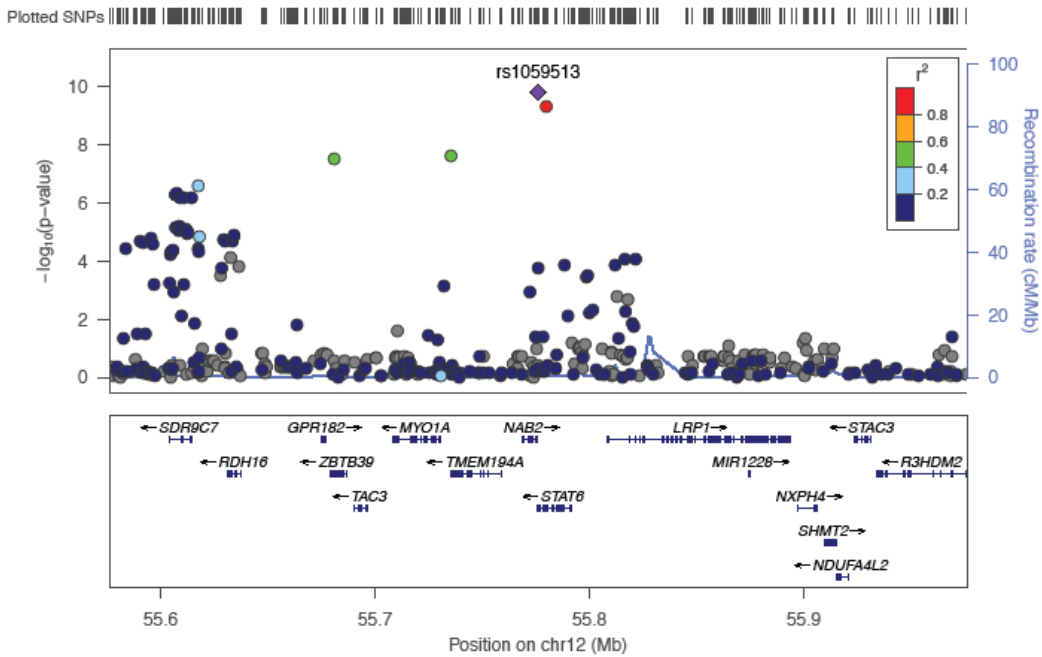
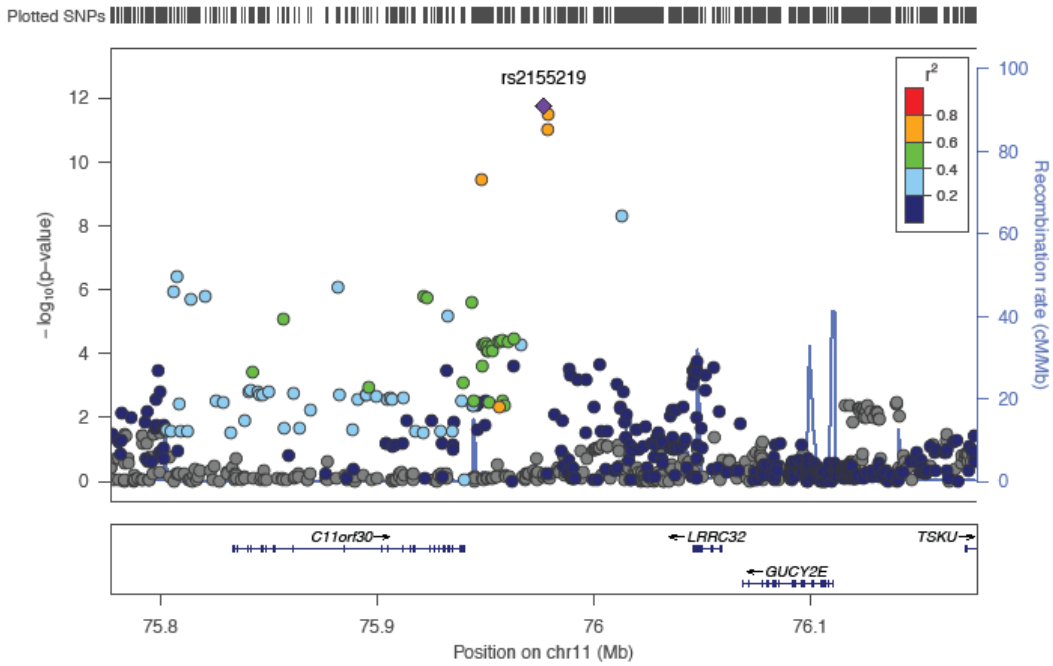
**Supplementary Note**

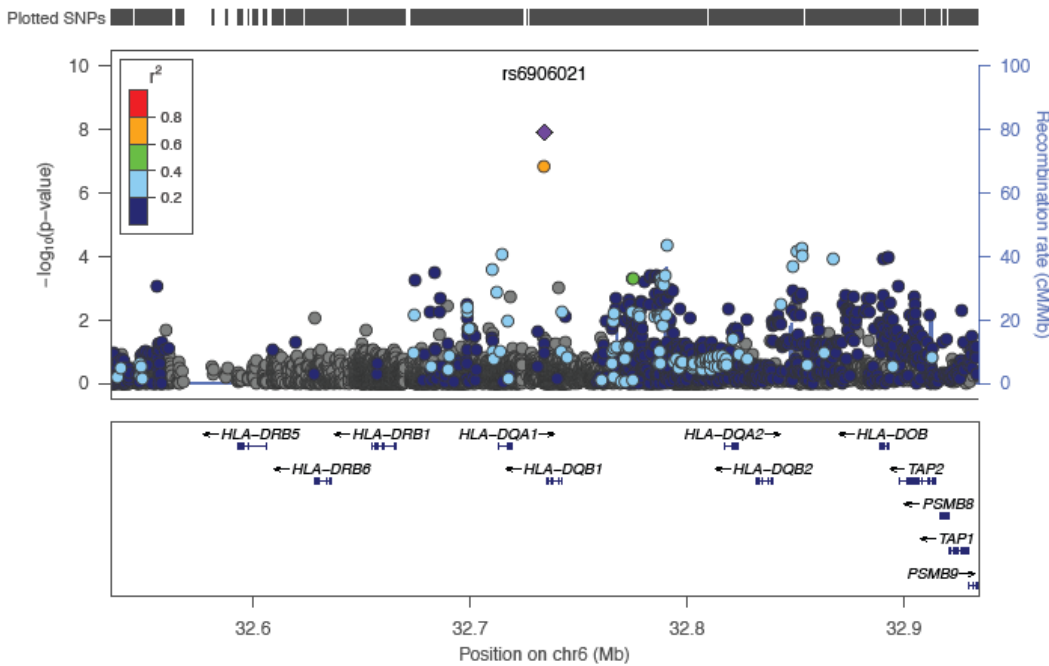
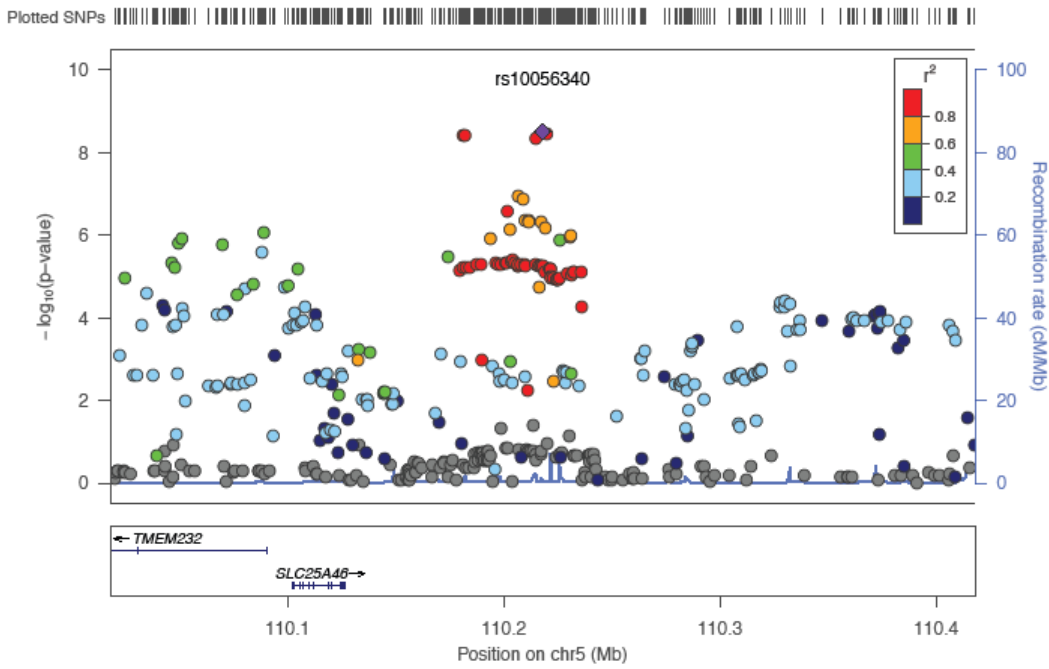
**References**

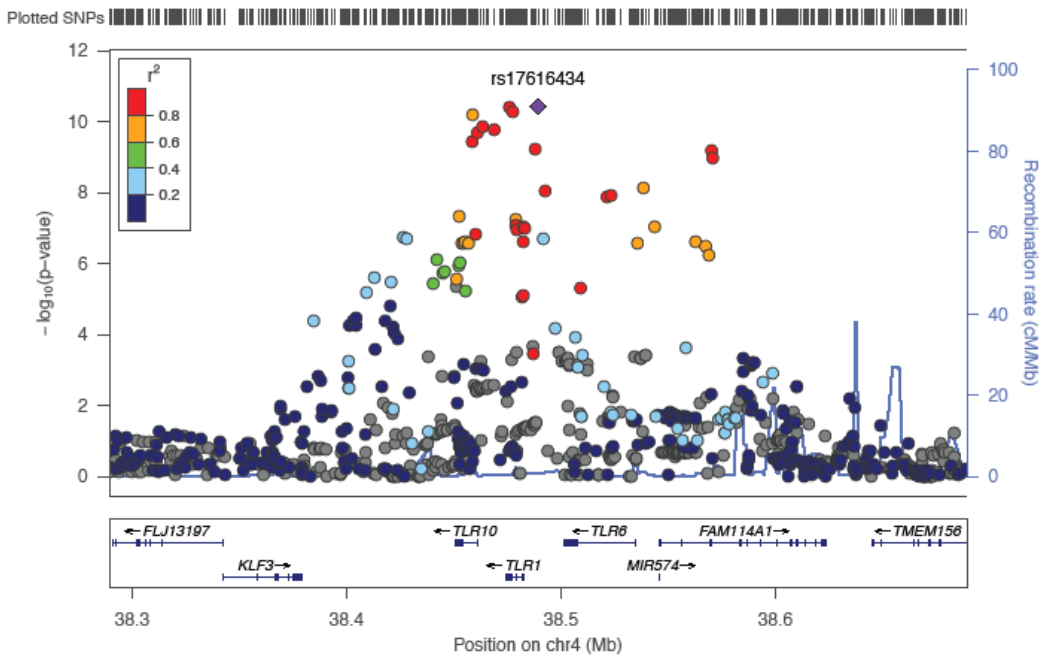
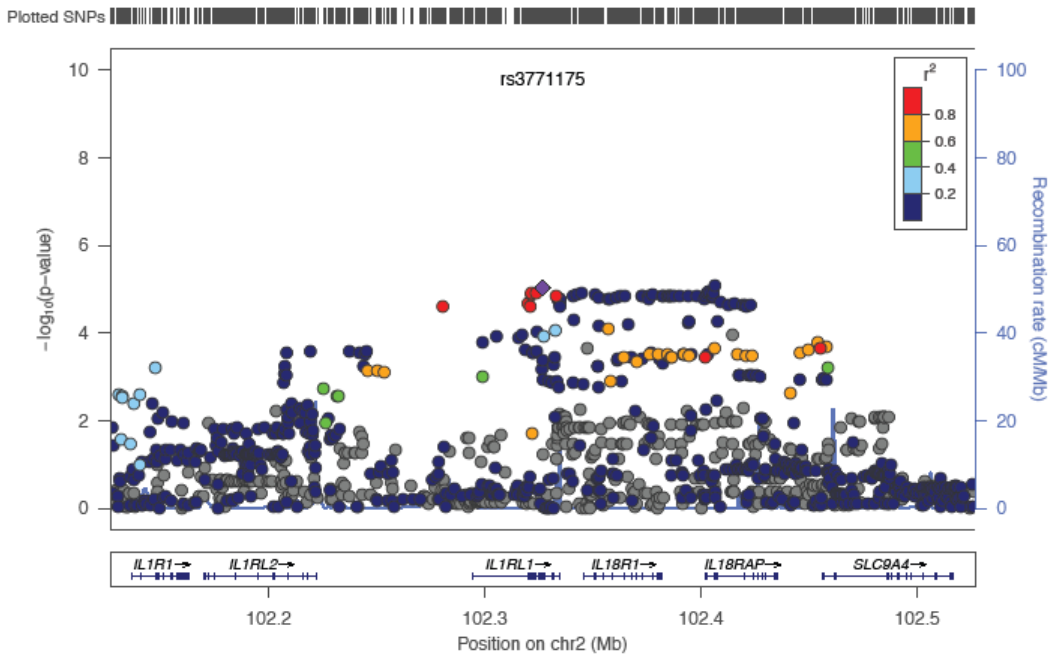
**Supplementary figure 1. QQ-plot for the discovery genome-wide association meta-analysis**



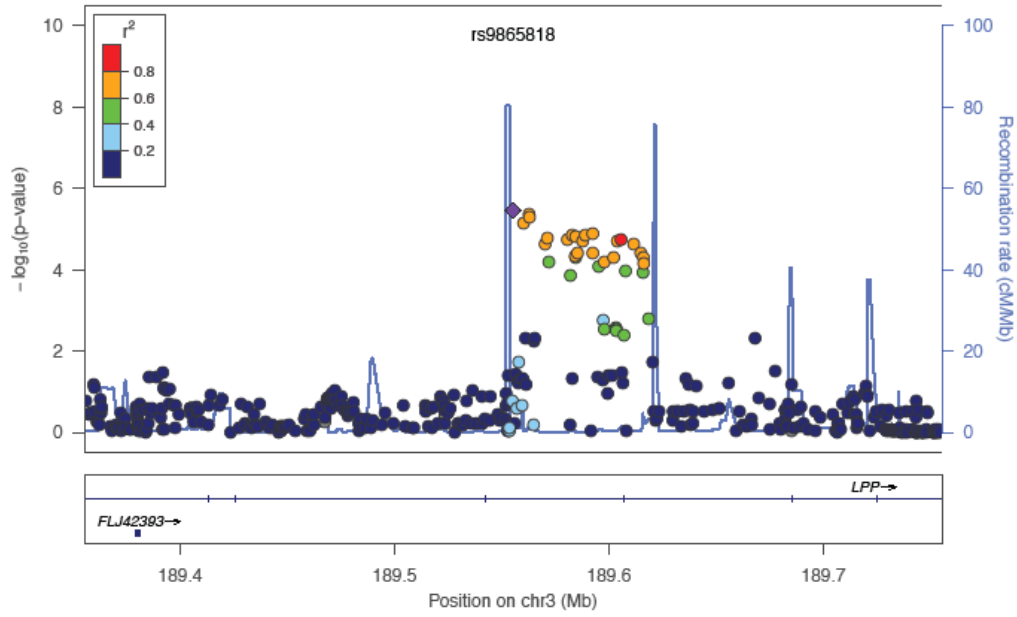
**Supplementary Figure 2. Regional association plots for the 10 genome-wide significant loci**



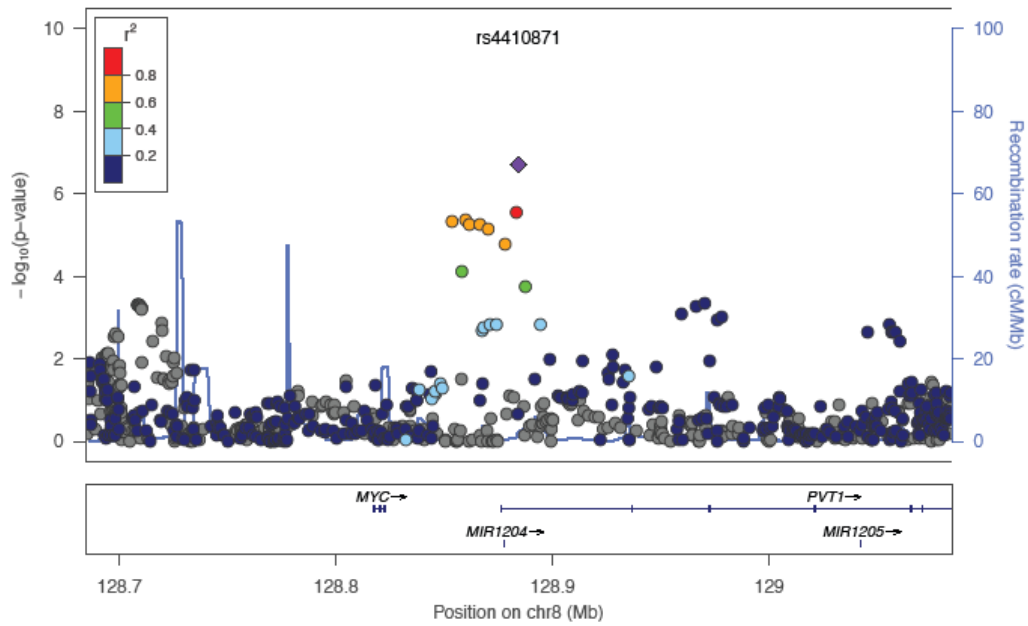


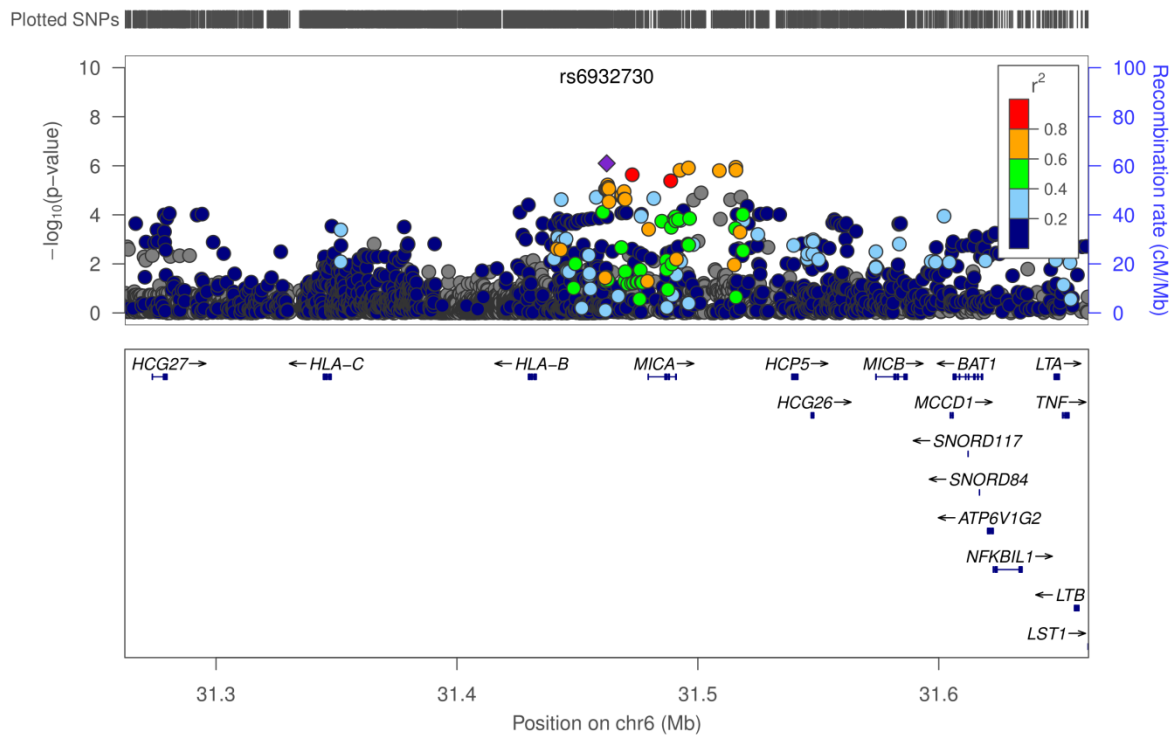
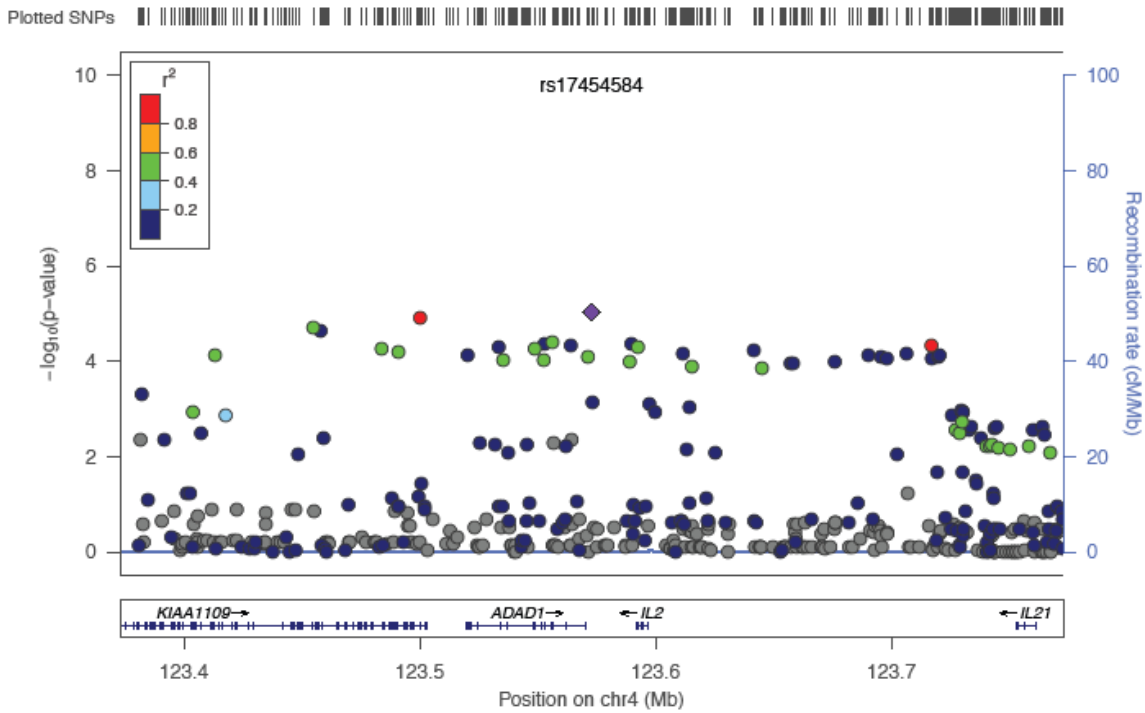


Plotted SNPs

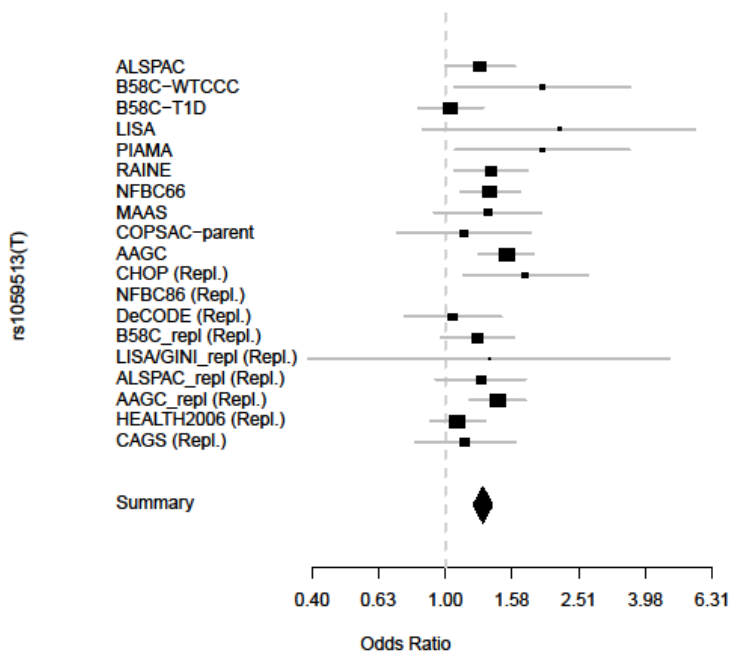
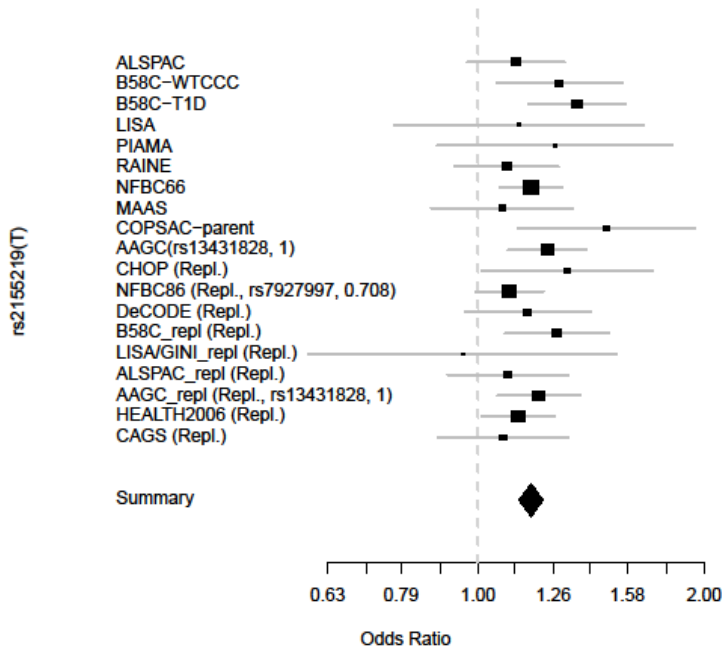


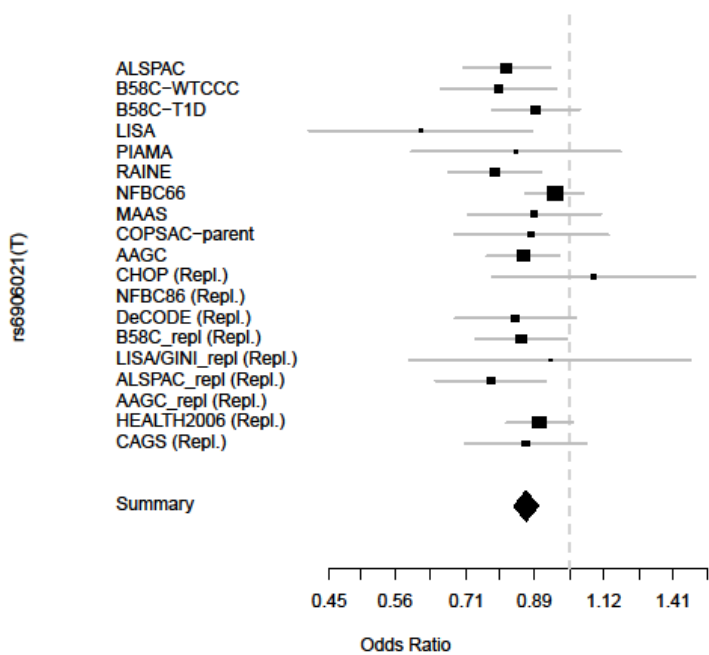
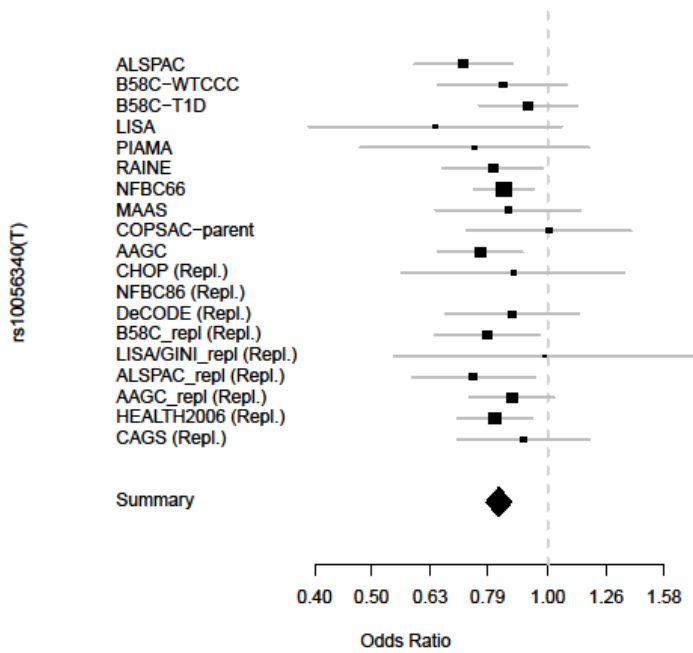
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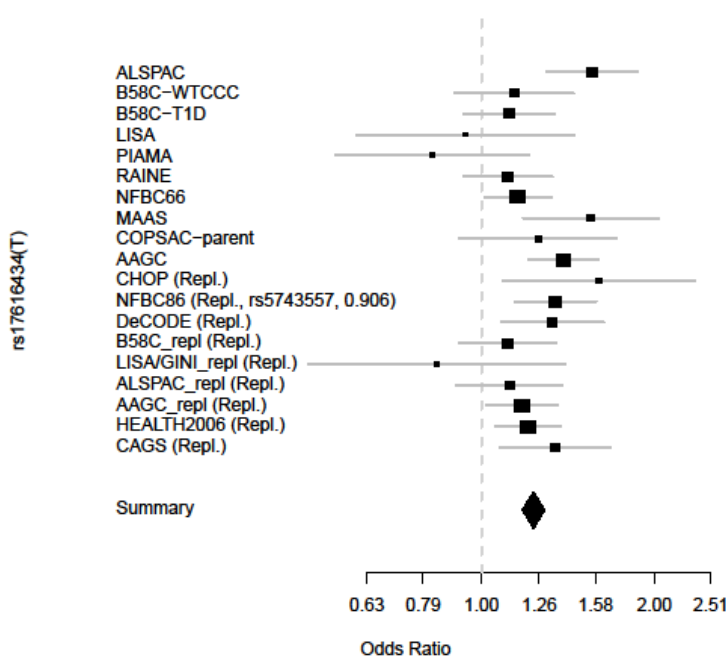
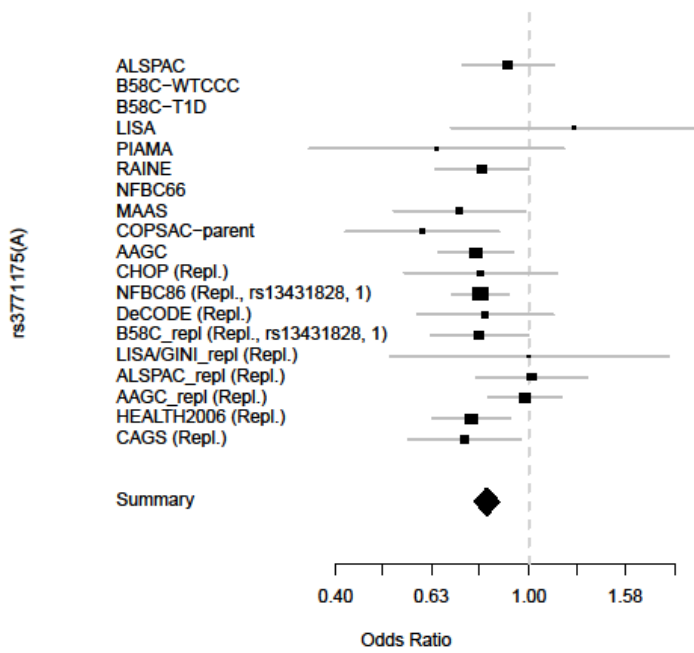


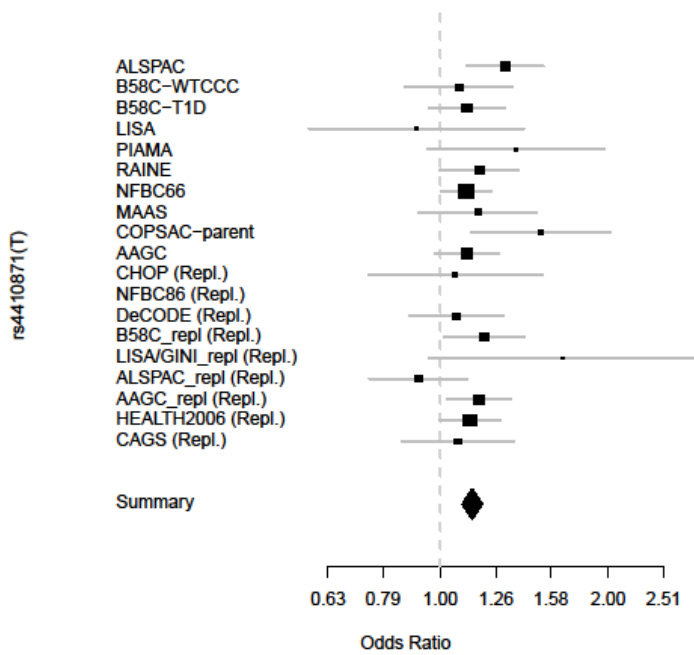
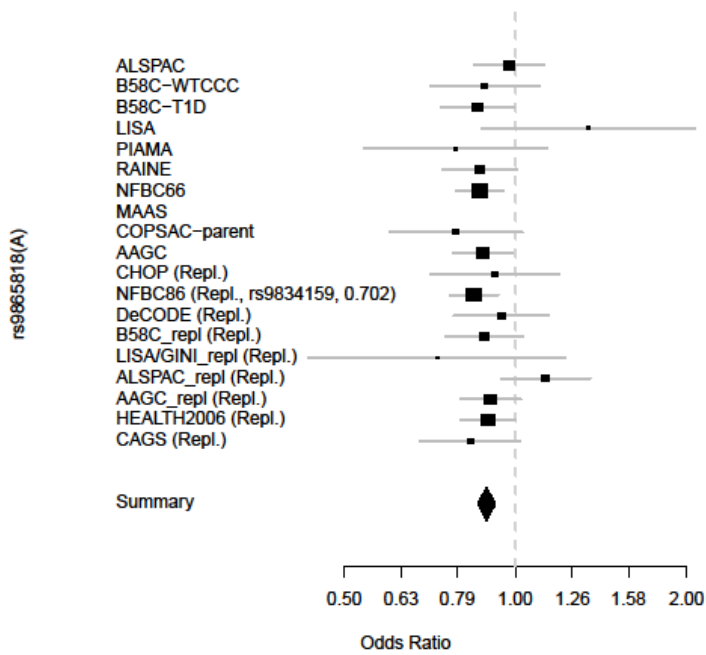


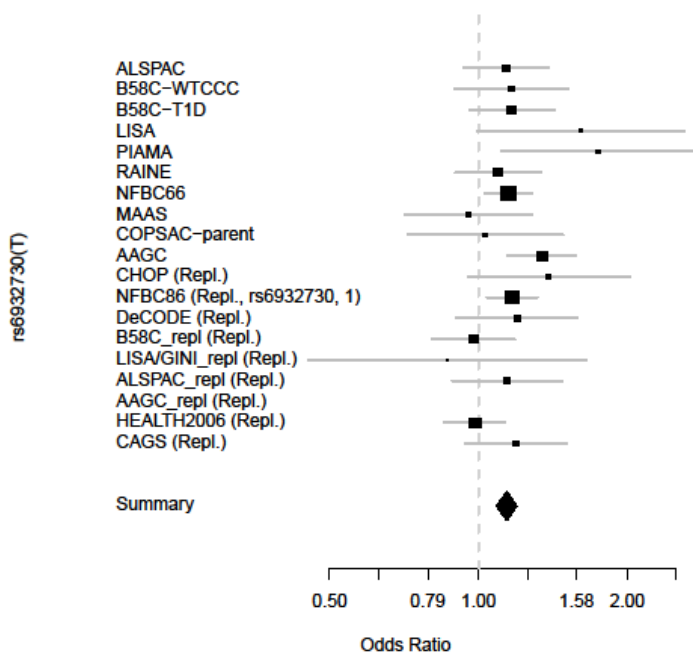
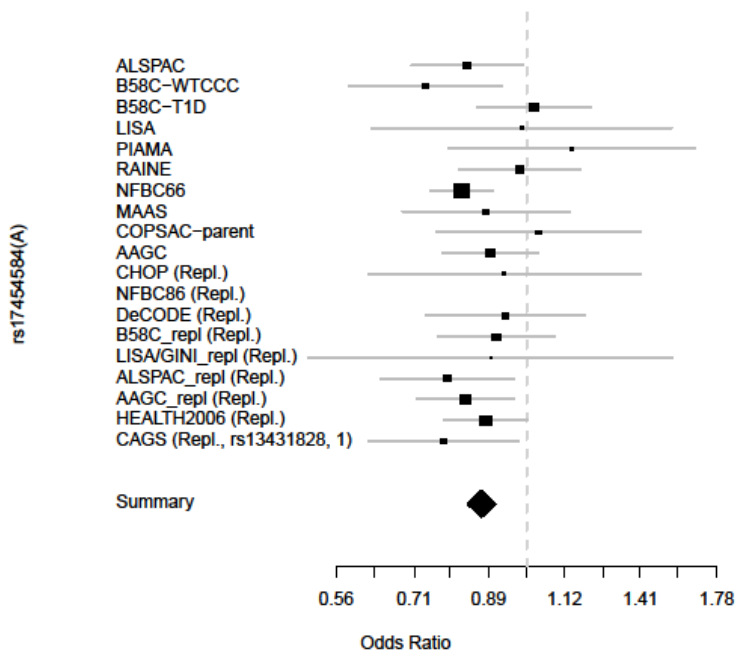
**Supplementary Figure 3. Forest plots of the association with sensitization for the 10 genome-wide significant SNPs for discovery and replication studies.** The effect allele is shown in brackets after the SNP name. For some SNPs a proxy was used in the replication studies, this is indicated by proxy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



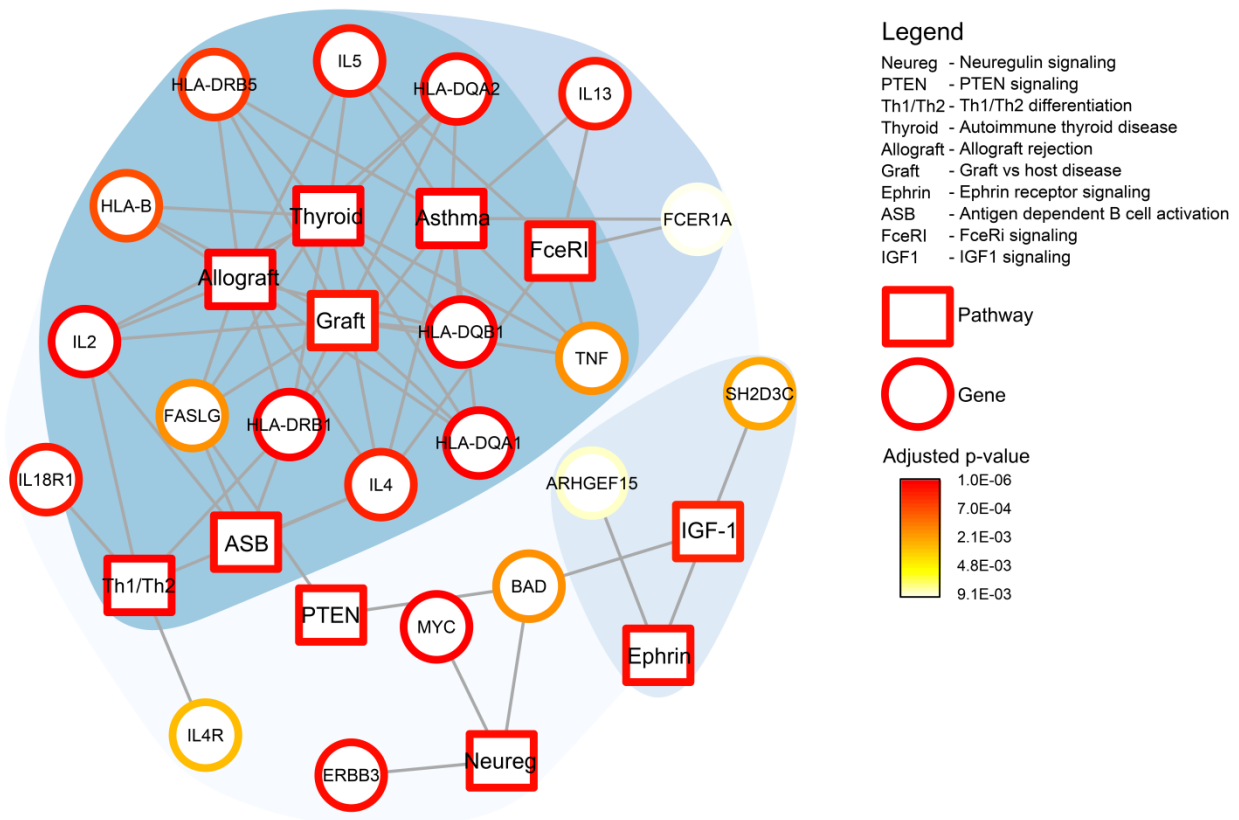








**Supplementary Figure 4. Bipartite network of the most significant genes and gene sets identified using pathway enrichment analysis (MAGENTA).** Individual genes associated with allergic sensitisation (Magenta gene score < 0.01) and involved in immune-related functions produced a cohesive cluster that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





**Supplementary 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   |
|---------------------------------|-------------------------|---|--|--------------|---------------------|--------------------------|--|
| <b>Discovery</b><br><b>AAGC</b> | Population based        | 2719                                      | Selected for asthma (1871 cases, 848 controls)     | 44%          | mean 45 yr (7 - 90) | SPT                      | cockroach mixture (QIMR, CAPS), <i>D. pteronyssinus</i> (QIMR, LIWA, Busselton, TAHS, CAPS, MESCA), <i>D. farinae</i> (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), <i>Aspergillus</i> spp. mixture (QIMR), <i>Alternaria</i> spp. mixture (QIMR), cows milk (QIMR, CAPS), egg white (QIMR, CAPS), egg yolk (CAPS), mould mixture (LIWA, Busselton), grass pollen mixture (LIWA), <i>Alternaria tenuis</i> (Busselton, TAHS, CAPS), <i>Aspergillus fumigatus</i> (Busselton, TAHS), grass mixture (Busselton), <i>Cladosporium herbarum</i> (TAHS), <i>Penicillium</i> spp. (TAHS), grass mixture (TAHS, CAPS), salmon (CAPS), tuna (CAPS), peanuts (CAPS) |
| <b>ALSPAC</b>                   | Birth cohort            | 2035                                      | Selected for asthma 650 cases, 650 controls)       | 52%          | 7.5 yr              | SPT                      | Dust mite, grass, cat, egg, peanut and mixed nuts  |
| <b>B58C (WTCCC)</b>             | Birth cohort            | 1320                                      | None   | 50%          | 45 yr               | Spec IgE (HYTEC)         | Dust mite, mixed grass, cat  |
| <b>B58C (T1DGC)</b>             | Birth cohort            | 2267                                      | None   | 47%          | 45 yr               | Spec IgE (HYTEC)         | Dust mite, mixed grass, cat  |
| <b>COPSAC parent</b>            | Parents of birth cohort | 558                                       | Selected for asthma (305 cases)                    | 45%          | 20-45 yr            | Spec IgE (ImmunoCAP)     | Cat, dog, horse, birch, timothy grass, <i>D. pteronyssinus</i> , mugwort, cladosporium   |
| <b>LISA</b>                     | Birth cohort            | 333                                       | None   | 58%          | 6 & 10 yr           | Spec IgE (RAST)          | Inhalant mix (SX1): <i>D. pteronyssinus</i> , cat, dog, rye grass, timothy, cladosporium, birch, mugwort.<br>Food mix (FX5): egg, peanuts, milk, codfish, wheat, soy.  |
| <b>MAAS</b>                     | Birth cohort            | 813                                       | None   | 54%          | 8, 11 yr            | SPT+spec IgE (ImmunoCAP) | SPT: <i>D. pteronyssinus</i> , cat, dog, mixed grass, mixed trees, mixed moulds, milk, egg and peanut; latex (11yr only)<br>SpecIgE: : House dust mite, cat, dog, timothy grass, milk, egg and peanut (age 8 years)  |

|  |                              |      |   |     |                   |                  |  |
|--|------------------------------|------|---|-----|-------------------|------------------|--|
| <b>NFBC 1966</b>                             | Birth cohort                 | 4292 | None  | 48% | 31 yr             | SPT              | Cat, birch, timothy grass, <i>D. pteronyssinus</i>   |
| <b>PIAMA</b>                                 | 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      | <i>D. pteronyssinus</i> , <i>D. farinae</i> , <i>Alternaria alternata</i> , mixed grass pollen, mixed tree pollen, cat, and dog, milk and egg  |
| <b>RAINE</b>                                 | 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  |
| <b>Replication<br/>AAGC-<br/>replication</b> | Population based             | 2222 | Selected for asthma (1210 cases, 1012 controls)   | 49% | Mean<br>47 (6-84) | SPT              | Cockroach mixture (QIMR), <i>D. pteronyssinus</i> (QIMR, LIWA, COPD, MNCA, TAHS), <i>D. farinae</i> (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), <i>Aspergillus</i> spp. mixture (QIMR), <i>Alternaria</i> spp. mixture (QIMR), cows milk (QIMR, MNCA), egg white (QIMR, MNCA), mould mixture (LIWA), grass pollen mixture (LIWA), ragweed (COPD, MNCA), <i>Cladosporium herbarum</i> (COPD, MNCA, TAHS), <i>Alternaria tenuis</i> (COPD, MNCA, TAHS), <i>Aspergillus fumigatus</i> (COPD, MNCA, TAHS), <i>Penicillium</i> spp. (COPD, TAHS), wheat (MNCA), peanut mix (MNCA), shrimp (MNCA), grass mixture (TAHS) |
| <b>ALSPAC-<br/>replication</b>               | Birth cohort                 | 1683 | None  | 49% | 7.5 yrs           | SPT              | Dust mite, grass, cat, egg, peanut and mixed nuts  |
| <b>B58C-<br/>replication</b>                 | Birth cohort                 | 1906 | None  | 50% | 45 yr             | Spec IgE (HYTEC) | Dust mite, mixed grass, cat  |
| <b>CAGS</b>                                  | Pediatric case control study | 806  | Selected for asthma   | 51% | 6-18 yrs          | SPT              | <i>D. pteronyssinus</i> , cat dander, dog dander, birch, ragweed, mixed grass, egg, peanut   |

|                              |                               |      |                     |     |                         |                 |   |
|------------------------------|-------------------------------|------|---------------------|-----|-------------------------|-----------------|---|
| <b>CHOP</b>                  | 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 |
| <b>deCODE</b>                | 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).   |
| <b>GINI/LISA-replication</b> | Birth cohort                  | 438  | None                | 52% | 6 & 10 yr               | Spec IgE (RAST) | Inhalant mix (SX1): D. pteronyssinus, cat, dog, rye grass, timothy, cladosporium, birch, mugwort.<br>Food mix (FX5): egg, peanuts, milk, codfish, wheat, soy.   |
| <b>Health2006</b>            | 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)  |
| <b>NFBC 1986</b>             | 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 |
|----------------------|---|--|--------------|--|-----------------|
| <b>AAGC</b>          | Combined SPT 3mm and or specIgE 3.5 IU/mL | SPT 3 mm above negative control                                  | 1871         | No SPT $\geq$ 1mm                                      | 848             |
|                      | SPT 3mm                                   | SPT 3 mm above negative control                                  | 1871         | No SPT $\geq$ 1mm                                      | 848             |
|                      | Spec IgE 3.5 IU/mL                        | NA   | NA           | NA   | NA              |
| <b>ALSPAC</b>        | Combined SPT 3mm and or specIgE 3.5 IU/mL | SPT 3 mm above negative control                                  | 512          | No SPT $\geq$ 1mm                                      | 1523            |
|                      | SPT 3mm                                   | SPT 3 mm above negative control                                  | 512          | No SPT $\geq$ 1mm                                      | 1523            |
|                      | Spec IgE 3.5 IU/mL                        | NA   | NA           | NA   | NA              |
| <b>B58C (WTCCC)</b>  | Combined SPT 3mm and or specIgE 3.5 IU/mL | Spec IgE $\geq$ 3.5 IU/mL  | 275          | No spec IgE $\geq$ 0.35 IU/mL                          | 1045            |
|                      | SPT 3mm                                   | NA   | NA           | NA   | NA              |
|                      | Spec IgE 3.5 IU/mL                        | Spec IgE $\geq$ 3.5 IU/mL  | 275          | No spec IgE $\geq$ 0.35 IU/mL                          | 1045            |
| <b>B58C (T1DGC)</b>  | Combined SPT 3mm and or specIgE 3.5 IU/mL | Spec IgE $\geq$ 3.5 IU/mL  | 475          | No spec IgE $\geq$ 0.35 IU/mL                          | 1792            |
|                      | SPT 3mm                                   | NA   | NA           | NA   | NA              |
|                      | Spec IgE 3.5 IU/mL                        | Spec IgE $\geq$ 3.5 IU/mL  | 475          | No spec IgE $\geq$ 0.35 IU/mL                          | 1792            |
| <b>COPSAC parent</b> | Combined SPT 3mm and or specIgE 3.5 IU/mL | Spec IgE $\geq$ 3.5 IU/mL  | 211          | No spec IgE $\geq$ 0.35 IU/mL                          | 283             |
|                      | SPT 3mm                                   | NA   | NA           | NA   | NA              |
|                      | Spec IgE 3.5 IU/mL                        | Spec IgE $\geq$ 3.5 IU/mL  | 211          | No spec IgE $\geq$ 0.35 IU/mL                          | 283             |
| <b>LISA</b>          | Combined SPT 3mm and or specIgE 3.5 IU/mL | Spec IgE $\geq$ 3.5 IU/mL  | 70           | No spec IgE $\geq$ 0.35 IU/mL                          | 263             |
|                      | SPT 3mm                                   | NA   | NA           | NA   | NA              |
|                      | Spec IgE 3.5 IU/mL                        | Spec IgE $\geq$ 3.5 IU/mL  | 70           | No spec IgE $\geq$ 0.35 IU/mL                          | 263             |
| <b>MAAS</b>          | Combined SPT 3mm and or specIgE 3.5 IU/mL | Spec IgE $\geq$ 3.5 IU/mL and/or SPT 3 mm above negative control | 319          | No spec IgE $\geq$ 0.35 IU/mL and/or no SPT $\geq$ 1mm | 441             |
|                      | SPT 3mm                                   | SPT 3 mm above negative control                                  | 315          | -  | 441             |
|                      | Spec IgE 3.5 IU/mL                        | Spec IgE $\geq$ 3.5 IU/mL  | 147          | -  | 441             |
| <b>NFBC 1966</b>     | Combined SPT 3mm and or specIgE 3.5 IU/mL | SPT 3 mm above negative control                                  | 1334         | No SPT $\geq$ 3mm                                      | 3102            |
|                      | SPT 3mm                                   | SPT 3 mm above negative control                                  | 1334         | No SPT $\geq$ 3mm                                      | 3102            |
|                      | Spec IgE 3.5 IU/mL                        | NA   | NA           | NA   | NA              |
| <b>PIAMA</b>         | Combined SPT 3mm and or specIgE 3.5 IU/mL | Spec IgE $\geq$ 3.5 IU/mL and/or SPT 3 mm above negative control | 104          | No spec IgE $\geq$ 0.35 IU/mL and/or no SPT $\geq$ 1mm | 176             |
|                      | SPT 3mm                                   | SPT 3 mm above negative control                                  | 52           | -  | 176             |
|                      | Spec IgE 3.5 IU/mL                        | Spec IgE $\geq$ 3.5 IU/mL  | 98           | -  | 176             |

|                           |   |  |      |  |      |
|---------------------------|---|--|------|--|------|
| <b>RAINE</b>              | 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   |
| <b>Replication</b>        |   |  |      |  |      |
| <b>AAGC-replication</b>   | 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   |
| <b>ALSPAC-replication</b> | 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   |
| <b>B58C-replication</b>   | 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 |
| <b>CAGS</b>               | 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   |
| <b>CHOP</b>               | 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   |
| <b>decode</b>             | 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   |
| <b>GINI/LISA</b>          | 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  |
| <b>Health2006</b>         | 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 |
| <b>NFBC 1986</b>          | 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)<br>Cohort                | Genotyping                                 |                                  | BEFORE IMPUTATION QUALITY CONTROL PER SUBJECT |                                 |   |   | BEFORE IMPUTATION QUALITY CONTROL PER SNP |                       |               |  | IMPUTATION                    |                                      |            | DATA ANALYSIS        |
|------------------------------|--|----------------------------------|---|---------------------------------|---|---|---|-----------------------|---------------|--|-------------------------------|--------------------------------------|------------|----------------------|
|                              | 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 |
| <b>Discovery</b>             |  |                                  |   |                                 |   |   |   |                       |               |  |                               |                                      |            |                      |
| <b>AAGC</b>                  | Illumina 370K (n=55) or 610K (n=2664)      | Illumina BeadStudio              | 0.95  | no                              | caucasians only                           | sexdiscrepancies, 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                |
| <b>ALSPAC</b>                | Illumina 317K or 610K                      | Illumina BeadStudio              | 0.97  | 0.34 & 0.36                     | MDS - eigenstrat adjusted caucasians only | sexdiscrepancies, related individuals   | 0.97                                      | 5 E-07                | 0.005         | no   | MACH 1.0                      | 22                                   | 36         | MACH2DAT             |
| <b>B58C WTCCC</b>            | Affymetrix500                              | Chiamo                           | 0.97  | 0.225 & 0.3                     | caucasians only                           | external discordance, relatives,sexdiscrepancies  | 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            |
| <b>B58C T1DGC</b>            | Illumina Infinium 550                      | Illuminus                        | 0.97  | 0.29 & 0.34                     | caucasians only                           | external discordance, relatives, sexdiscrepancies   | 0.95                                      | 1 E-07                | 0.01          | no   | MACH                          | 21                                   | 35         | probAbel             |
| <b>COPSAC</b>                | 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              |
| <b>LISA</b>                  | 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              |
| <b>MAAS</b>                  | 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              |
| <b>NFBC 1966</b>             | 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              |
| <b>PIAMA</b>                 | 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              |
| <b>RAINE</b>                 | Illumina 660K                              | Illumina Beadstudio              | 0.95  | 0.32 & 0.36                     | Eigenstrat adjusted                       | yes - IBD check and exclude family relations, sex discrepancies   | 0.95                                      | 5.7 E-07              | 0.01          | no   | MACH                          | 22                                   | 36         | MACH2DAT             |
| <b>Replication in silico</b> |  |                                  |   |                                 |   |   |   |                       |               |  |                               |                                      |            |                      |
| <b>B58C</b>                  | Illumina 550K/610K                         | Beadstudio                       | 0.97  | no                              | caucasians only                           | no  | 0.95                                      | 1 E-04                | 0.01          | no   | MACH                          | 21                                   | 35         | probAbel             |
| <b>ALSPAC</b>                | Illumina HumanHap550 quad                  | Illumina BeadStudio              | 0.97  | 0.32 - 0.345 or 0.0.9731 - 0.33 | caucasians only                           | sexdiscrepancies, cryptic relatedness, replicates <80% IBD  | 0.95                                      | 5 E-07                | 0.01          | no   | Mach 1.0.16                   | 22                                   | 36         | MACH2DAT             |
| <b>CHOP</b>                  | 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              |
| <b>deCODE</b>                | 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              |
| <b>GINI/LISA</b>             | Affymetrix 5.0 Affymetrix 6.0              | BRLMM-P (5.0), BIRDSEED V2 (6.0) | 0.95  | Mean +/- 4 SD                   | caucasians only                           | sexdiscrepancies  | 0.95                                      | 1 E-05                | 0.01          | no   | IMPUTE v2                     | 22                                   | 36         | SNPTEST              |
| <b>NFBC 1986</b>             | 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)<br>Cohort              | Genotyping  |                            | QUALITY CONTROL PER SUBJECT |                            |   | QUALITY CONTROL PER SNP |                              |               | DATA ANALYSIS        |
|----------------------------|---|----------------------------|-----------------------------|----------------------------|---|-------------------------|------------------------------|---------------|----------------------|
|                            | 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 |
| <b>Replication de novo</b> |   |                            |                             |                            |   |                         |                              |               |                      |
| <b>AAGC-replication</b>    | Sequenom MassArray  | Sequenom                   | 0.98                        | caucasians only (reported) | Sex discrepancies                           | 0.98                    | 1                            | NA            | PLINK                |
| <b>CAGS</b>                | sequenom and taqman   |                            | 0.97                        | caucasians only            | no  | 0.97                    | 2 out of 26                  | 0.09          | SNPTEST              |
| <b>Health2006</b>          | 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**

| Region  | SNP        | Position (bp) | Nearest gene          | Eff all ele | Alt all ele | Effect allele freq. | Discovery (stage 1) |                | Replication (stage2) |                | Combined         |                  | Het P/<br><i>I</i> <sup>2</sup> (%) |
|---|------------|---------------|-----------------------|-------------|-------------|---------------------|---------------------|----------------|----------------------|----------------|------------------|------------------|-------------------------------------|
|   |            |               |                       |             |             |                     | OR (95% CI)         | <i>P</i> value | OR (95% CI)          | <i>P</i> value | OR (95% CI)      | <i>P</i> value   |                                     |
| <b>Top loci from discovery analysis replicating in stage 2 and genome wide significant in the combined analysis</b> |            |               |                       |             |             |                     |                     |                |                      |                |                  |                  |                                     |
| 11q13.5   | rs2155219  | 75976842      | <i>C11orf30</i>       | t           | g           | 0.47                | 1.20 (1.14-1.24)    | <b>1.8E-12</b> | 1.15 (1.09-1.21)     | 1.1E-07        | 1.18 (1.13-1.22) | <b>1.4E-18</b>   | 0.57/0                              |
| 12q13.3   | rs1059513  | 55775976      | <i>STAT6</i>          | t           | c           | 0.90                | 1.34 (1.22-1.47)    | <b>1.6E-10</b> | 1.24 (1.13-1.37)     | 1E-05          | 1.30 (1.21-1.39) | <b>1.0E-14</b>   | 0.25/17                             |
| 5q22.1  | rs10056340 | 110217951     | <i>SLC25A46</i>       | t           | g           | 0.83                | 0.82 (0.77-0.88)    | <b>3.2E-09</b> | 0.83 (0.77-0.90)     | 4.4E-06        | 0.83 (0.78-0.87) | <b>5.2E-14</b>   | 0.93/0                              |
| 6p21.32   | rs6906021  | 32734289      | <i>HLADQB1</i>        | t           | c           | 0.55                | 0.86 (0.82-0.91)    | <b>1.3E-08</b> | 0.87 (0.81-0.93)     | 4.8E-05        | 0.87 (0.83-0.90) | <b>2.2E-12</b>   | 0.51/0                              |
| 2q12.1  | rs3771175  | 102326642     | <i>IL1RL1/IL18R1</i>  | 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) | <b>4.9E-11</b>   | 0.39/5                              |
| 4p14  | rs17616434 | 38489271      | <i>TLR1/6/10</i>      | t           | c           | 0.78                | 1.24 (1.16-1.32)    | <b>3.8E-11</b> | 1.22 (1.15-1.31)     | 3.8E-10        | 1.23 (1.18-1.29) | <b>5.2 E-11*</b> | 0.04/40                             |
| 3q28  | rs9865818  | 189555207     | <i>LPP</i>            | 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) | <b>2.7E-10</b>   | 0.49/0                              |
| 8q24.21   | rs4410871  | 128884211     | <i>MYC/PVT1</i>       | 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) | <b>5.4E-10</b>   | 0.45/1                              |
| 4q27  | rs17454584 | 123572882     | <i>IL2/ADAD1</i>      | 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) | <b>5.5E-10</b>   | 0.74/0                              |
| 6p21.33   | rs6932730  | 31462161      | <i>HLA-B/MICA</i>     | 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) | <b>4.2E-08</b>   | 0.26/16                             |
| <b>Top loci from discovery analysis not replicating in stage2</b>   |            |               |                       |             |             |                     |                     |                |                      |                |                  |                  |                                     |
| 2q13  | rs11122895 | 112186626     | <i>ANAPC1</i>         | 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      | <i>COL21A1</i>        | 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     | <i>FASLG</i>          | 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      | <i>ORCL3/AKIRIN2</i>  | 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     | <i>IL18RAP/SLC9A4</i> | 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      | <i>HS3ST4</i>         | 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       | <i>CD9</i>            | 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      | <i>FAM19A5</i>        | 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      | <i>C15orf53</i>       | 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     | <i>SLU7</i>           | 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      | <i>OFCC1</i>          | 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 Cochran's Q statistic

\* The *P* value was calculated by random effects model due to evidence of heterogeneity between studies (Heterogeneity *P* for Cochran'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<sup>1</sup> 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).

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

*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

| SNP        | GENE                              | Alleles |       | deCODE: white blood cells |       |                | deCODE: adipose tissue |       |                | ALSPAC: LCLs |       |                |       | KORA: whole blood |       |                 |       |
|------------|-----------------------------------|---------|-------|---------------------------|-------|----------------|------------------------|-------|----------------|--------------|-------|----------------|-------|-------------------|-------|-----------------|-------|
|            |                                   | Effect  | Other | BETA                      | SE    | PVALUE         | BETA                   | SE    | PVALUE         | BETA         | SE    | PVALUE         | R2    | BETA              | SE    | PVALUE          | R2    |
| rs10056340 | <i>CAMK4</i>                      | T       | G     | NA                        | NA    | NA             | NA                     | NA    | NA             | -0.214       | 0.063 | <b>0.0007</b>  | 0.012 | 0.003             | 0.012 | 0.8017          | 0.039 |
| rs1059513  | <i>TMEM194A</i>                   | T       | C     | 0.167                     | 0.081 | 0.0470         | 0.328                  | 0.092 | <b>0.0006</b>  | NA           | NA    | NA             | NA    | NA                | NA    | NA              | NA    |
| rs1059513  | <i>NAB2_STAT6</i>                 | T       | C     | 0.260                     | 0.081 | 0.0018         | 0.473                  | 0.091 | <b>4.7e-07</b> | NA           | NA    | NA             | NA    | NA                | NA    | NA              | NA    |
| rs1059513  | <i>NACA</i>                       | T       | C     | 0.059                     | 0.083 | 0.4900         | 0.338                  | 0.091 | <b>0.0004</b>  | -0.181       | 0.071 | 0.0110         | 0.007 | -0.113            | 0.086 | 0.1880          | 0.009 |
| rs1059513  | <i>STAT6</i>                      | T       | C     | NA                        | NA    | NA             | NA                     | NA    | NA             | 0.430        | 0.070 | <b>7.6E-10</b> | 0.039 | 0.188             | 0.043 | <b>1.6E-05</b>  | 0.027 |
| rs17616434 | <i>AK023259</i>                   | T       | C     | -0.252                    | 0.060 | <b>4.4E-05</b> | -0.230                 | 0.065 | <b>0.0006</b>  | NA           | NA    | NA             | NA    | NA                | NA    | NA              | NA    |
| rs17616434 | <i>FAM114A1</i>                   | T       | C     | -0.306                    | 0.058 | <b>2.7E-07</b> | -0.283                 | 0.066 | <b>3.7E-05</b> | -0.400       | 0.053 | <b>3.5E-14</b> | 0.057 | 0.000             | 0.007 | 0.9838          | 0.006 |
| rs17616434 | <i>TLR1</i>                       | T       | C     | 0.234                     | 0.061 | <b>0.0002</b>  | 0.139                  | 0.067 | 0.0440         | -0.212       | 0.053 | <b>7.1E-05</b> | 0.016 | -0.035            | 0.055 | 0.5235          | 0.003 |
| rs17616434 | <i>TLR10</i>                      | T       | C     | 0.070                     | 0.060 | 0.2500         | 0.044                  | 0.067 | 0.5200         | -0.569       | 0.051 | <b>2.8E-29</b> | 0.118 | 0.052             | 0.010 | <b>1.7E-07</b>  | 0.047 |
| rs17616434 | <i>TLR6</i>                       | T       | C     | 0.281                     | 0.059 | <b>4.1E-06</b> | 0.034                  | 0.066 | 0.6200         | -0.706       | 0.049 | <b>7.5E-48</b> | 0.183 | 0.046             | 0.021 | 0.0259          | 0.022 |
| rs2155219  | <i>C11orf30</i>                   | T       | G     | -0.577                    | 0.053 | <b>4.2E-26</b> | -0.476                 | 0.058 | <b>2.2E-15</b> | NA           | NA    | NA             | NA    | NA                | NA    | NA              | NA    |
| rs2155219  | <i>LRRC32</i>                     | T       | G     | -0.252                    | 0.054 | <b>7.1E-06</b> | 0.070                  | 0.061 | 0.2700         | -0.083       | 0.048 | 0.0835         | 0.003 | -0.016            | 0.007 | 0.0236          | 0.007 |
| rs3771175  | <i>IL18RAP</i>                    | T       | A     | -0.551                    | 0.082 | <b>6.2E-11</b> | 0.183                  | 0.088 | 0.0450         | 0.102        | 0.070 | 0.1461         | 0.002 | -0.335            | 0.044 | <b>7.3E-14</b>  | 0.077 |
| rs3771175  | <i>MFS09</i>                      | T       | A     | -0.465                    | 0.083 | <b>5.4E-08</b> | 0.022                  | 0.091 | 0.8200         | -0.063       | 0.070 | 0.3722         | 0.001 | -0.035            | 0.014 | 0.0129          | 0.009 |
| rs6906021  | <i>GPM3_NOTCH4</i>                | T       | C     | 0.087                     | 0.054 | 0.1200         | 0.399                  | 0.060 | <b>1.8E-10</b> | NA           | NA    | NA             | NA    | NA                | NA    | NA              | NA    |
| rs6906021  | <i>HLA-DPB1</i>                   | T       | C     | -0.260                    | 0.056 | <b>7.5E-06</b> | -0.273                 | 0.062 | <b>2.2E-05</b> | -0.106       | 0.046 | 0.0222         | 0.006 | -0.062            | 0.023 | 0.0086          | 0.013 |
| rs6906021  | <i>HLA-DQA1</i>                   | T       | C     | 0.864                     | 0.045 | <b>2.5E-77</b> | 0.704                  | 0.056 | <b>3.1E-34</b> | 0.397        | 0.045 | <b>5.9E-19</b> | 0.077 | 0.455             | 0.031 | <b>5.1E-42</b>  | 0.224 |
| rs6906021  | <i>HLA-DQA2</i>                   | T       | C     | -0.110                    | 0.057 | 0.0640         | -0.061                 | 0.063 | 0.3500         | -0.183       | 0.046 | <b>8.1E-05</b> | 0.016 | -0.013            | 0.008 | 0.1097          | 0.011 |
| rs6906021  | <i>HLA-DQB1</i>                   | T       | C     | 0.758                     | 0.047 | <b>9.7E-55</b> | 0.390                  | 0.061 | <b>8.2E-10</b> | NA           | NA    | NA             | NA    | -0.920            | 0.036 | <b>3.4E-104</b> | 0.472 |
| rs6906021  | <i>HLA-DQB2</i>                   | T       | C     | 0.256                     | 0.054 | <b>5.1E-06</b> | 0.154                  | 0.062 | 0.0180         | NA           | NA    | NA             | NA    | 0.029             | 0.011 | 0.0082          | 0.012 |
| rs6906021  | <i>HLA-DRB1</i>                   | T       | C     | NA                        | NA    | NA             | NA                     | NA    | NA             | 0.552        | 0.043 | <b>5.9E-38</b> | 0.149 | NA                | NA    | NA              | NA    |
| rs6906021  | <i>HLA-DRB1_HLA-DRB5</i>          | T       | C     | 0.396                     | 0.054 | <b>1.4E-12</b> | 0.503                  | 0.060 | <b>6.7E-16</b> | NA           | NA    | NA             | NA    | NA                | NA    | NA              | NA    |
| rs6906021  | <i>HLA-DRB1_HLA-DRB5_HLA-DRB6</i> | T       | C     | -0.427                    | 0.055 | <b>5.2E-14</b> | -0.273                 | 0.062 | <b>2.2E-05</b> | NA           | NA    | NA             | NA    | NA                | NA    | NA              | NA    |
| rs6906021  | <i>HLA-DRB5</i>                   | T       | C     | 0.411                     | 0.053 | <b>4.6E-14</b> | 0.416                  | 0.061 | <b>5.9E-11</b> | 0.341        | 0.045 | <b>3.9E-14</b> | 0.057 | -0.172            | 0.021 | <b>9.3E-16</b>  | 0.088 |
| rs6906021  | <i>HSPA1B</i>                     | T       | C     | NA                        | NA    | NA             | NA                     | NA    | NA             | NA           | NA    | NA             | NA    | -0.085            | 0.024 | <b>0.0004</b>   | 0.022 |
| rs6906021  | <i>PSMB9</i>                      | T       | C     | -0.253                    | 0.056 | <b>1.2E-05</b> | -0.158                 | 0.062 | 0.0140         | -0.192       | 0.046 | <b>3.3E-05</b> | 0.018 | -0.043            | 0.026 | 0.0965          | 0.026 |
| rs6906021  | <i>TAP2</i>                       | T       | C     | 0.059                     | 0.057 | 0.3200         | -0.168                 | 0.063 | 0.0093         | -0.345       | 0.045 | <b>2.2E-14</b> | 0.058 | -0.079            | 0.019 | <b>2.3E-05</b>  | 0.027 |
| rs6932730  | <i>APOM</i>                       | T       | C     | -0.169                    | 0.077 | 0.0340         | -0.341                 | 0.083 | <b>7.8E-05</b> | NA           | NA    | NA             | NA    | -0.009            | 0.012 | 0.4498          | 0.004 |
| rs6932730  | <i>C5orf13</i>                    | T       | C     | NA                        | NA    | NA             | NA                     | NA    | NA             | -0.249       | 0.065 | <b>0.0001</b>  | 0.016 | NA                | NA    | NA              | NA    |
| rs6932730  | <i>HLA-B_HLA-C_HLA-Cw*050x</i>    | T       | C     | -0.288                    | 0.076 | <b>0.0002</b>  | -0.218                 | 0.084 | 0.0120         | NA           | NA    | NA             | NA    | NA                | NA    | NA              | NA    |

|           |               |   |   |       |       |                |        |       |                |        |       |                |       |        |       |                |       |
|-----------|---------------|---|---|-------|-------|----------------|--------|-------|----------------|--------|-------|----------------|-------|--------|-------|----------------|-------|
| rs6932730 | <i>HLA-C</i>  | T | C | NA    | NA    | NA             | NA     | NA    | NA             | NA     | NA    | NA             | NA    | 0.411  | 0.059 | <b>5.7E-12</b> | 0.063 |
| rs6932730 | <i>HSPA1B</i> | T | C | 0.205 | 0.081 | 0.0140         | 0.494  | 0.082 | <b>4.7E-09</b> | NA     | NA    | NA             | NA    | -0.001 | 0.029 | 0.9812         | 0.005 |
| rs6932730 | <i>IER3</i>   | T | C | NA    | NA    | NA             | NA     | NA    | NA             | -0.260 | 0.064 | <b>4.4E-05</b> | 0.017 | 0.047  | 0.032 | 0.1402         | 0.006 |
| rs6932730 | <i>LST1</i>   | T | C | 0.011 | 0.078 | 0.8900         | -0.079 | 0.085 | 0.3800         | -0.313 | 0.064 | <b>9.1E-07</b> | 0.025 | 0.038  | 0.025 | 0.1384         | 0.025 |
| rs6932730 | <i>MICB</i>   | T | C | 0.516 | 0.075 | <b>2.3E-11</b> | 0.514  | 0.083 | <b>2.4E-09</b> | NA     | NA    | NA             | NA    | 0.076  | 0.027 | 0.0044         | 0.017 |
| rs6932730 | <i>NEU1</i>   | T | C | 0.172 | 0.078 | 0.0340         | 0.025  | 0.085 | 0.7800         | 0.219  | 0.065 | <b>0.0008</b>  | 0.012 | 0.001  | 0.019 | 0.9784         | 0.022 |
| rs6932730 | <i>TAP2</i>   | T | C | NA    | NA    | NA             | NA     | NA    | NA             | -0.284 | 0.065 | <b>1.1E-05</b> | 0.02  | NA     | NA    | NA             | NA    |
| rs6932730 | <i>VAR52</i>  | T | C | NA    | NA    | NA             | NA     | NA    | NA             | -0.223 | 0.064 | <b>0.0005</b>  | 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 |                  |         |                                  |          |                                  |           |
|--|------------------|---------|----------------------------------|----------|----------------------------------|-----------|
| SNP  | GENE             | Probe   | Allelic_expression<br>_direction | B-cells  | Allelic_expression<br>_direction | Monocytes |
|  |                  |         |                                  | P VALUE  |                                  | P VALUE   |
| rs17616434   | <i>HS.214235</i> | 2120056 | -                                | -        | C>T                              | 0.002     |
| rs1059513  | <i>CYP27B1</i>   | 2900725 | T>C                              | 0.003    | -                                | -         |
| rs1059513  | <i>STAT6</i>     | 1660397 | T>C                              | 0.007    | T>C                              | 6.4 E-05  |
| rs1059513  | <i>RNF41</i>     | 1090433 | -                                | -        | T>C                              | 0.007     |
| rs1059513  | <i>STAT2</i>     | 130519  | -                                | -        | T>C                              | 0.008     |
| rs17454584   | <i>IL2</i>       | 4290356 | G>A                              | 0.002    | -                                | -         |
| rs6906021  | <i>HSPA1B</i>    | 3850433 | C>T                              | 3.9 E-04 | -                                | -         |
| rs6906021  | <i>TAP2</i>      | 3940477 | C>T                              | 0.002    | C>T                              | 4.8 E-04  |
| rs6906021  | <i>ATF6B</i>     | 4640110 | C>T                              | 0.004    | -                                | -         |
| rs6906021  | <i>VAR5</i>      | 6980100 | T>C                              | 0.009    | -                                | -         |
| rs6906021  | <i>BRD2</i>      | 1340475 | -                                | -        | C>T                              | 0.007     |
| rs6906021  | <i>CLIC1</i>     | 3450072 | -                                | -        | C>T                              | 0.007     |
| rs3771175  | <i>IL1R1</i>     | 240274  | A>T                              | 0.001    | -                                | -         |
| rs9865818  | <i>LPP</i>       | 6350711 | G>A                              | 4.0 E-06 | -                                | --        |
| rs9865818  | <i>LPP</i>       | 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 |                 | <i>STAT6</i>               | 5.19E-13            |
| rs17454584 | rs17388568 | 0.74                | 4   | 123548812  | A            | G            | 0.30 | <i>ADAD1</i>    | <i>HBEGF</i>               | 3.51E-06            |
| rs17454584 | rs925549   | 0.55                | 4   | 123750443  | C            | T            | 0.34 |                 | <i>HBEGF</i>               | 4.66E-06            |
| rs17454584 | rs6829845  | 0.54                | 4   | 123730216  | A            | G            | 0.34 |                 | <i>HBEGF</i>               | 9.88E-06            |
| rs17616434 | rs2101521  | 0.91                | 4   | 38487946   | A            | G            | 0.22 |                 | <i>RPL32P3,TLR6</i>        | 8.32E-07            |
| rs17616434 | rs6835514  | 0.80                | 4   | 38570775   | G            | A            | 0.25 | <i>FAM114A1</i> | <i>TLR6</i>                | 5.70E-07            |
| rs17616434 | rs5743592  | 0.72                | 4   | 38479458   | G            | A            | 0.19 | <i>TLR1</i>     | <i>DNAJC7,RPL32P3,TLR6</i> | 1.37E-08            |
| rs17616434 | rs11722813 | 0.72                | 4   | 38487164   | T            | C            | 0.19 |                 | <i>DNAJC7,RPL32P3,TLR6</i> | 1.89E-08            |
| rs17616434 | rs17582830 | 0.66                | 4   | 38543822   | G            | A            | 0.21 |                 | <i>DNAJC7,TLR6,ZNF236</i>  | 3.31E-07            |
| rs17616434 | rs11466640 | 0.63                | 4   | 38455298   | A            | G            | 0.18 | <i>TLR10</i>    | <i>DNAJC7,TLR6</i>         | 1.64E-07            |
| rs17616434 | rs11096956 | 0.55                | 4   | 38452575   | A            | C            | 0.22 | <i>TLR10</i>    | <i>TLR6</i>                | 5.64E-07            |
| rs3771175  | rs3771158  | 0.74                | 2   | 102376326  | G            | A            | 0.18 | <i>IL18R1</i>   | <i>NPAT</i>                | 5.00E-06            |
| rs3771175  | rs10197310 | 0.71                | 2   | 102386462  | A            | T            | 0.18 |                 | <i>NPAT</i>                | 2.46E-06            |
| rs3771175  | rs10210176 | 0.71                | 2   | 102445948  | A            | C            | 0.18 |                 | <i>NPAT</i>                | 3.06E-06            |
| rs3771175  | rs11687768 | 0.71                | 2   | 102392170  | G            | A            | 0.18 |                 | <i>NPAT</i>                | 4.91E-06            |
| rs3771175  | rs10202813 | 0.71                | 2   | 102386172  | T            | G            | 0.18 |                 | <i>NPAT</i>                | 7.58E-06            |
| rs6932730  | rs2394999  | 0.74                | 6   | 31508914   | G            | A            | 0.20 |                 | <i>COL7A1,HCG4,MICB</i>    | 4.37E-07            |
| rs6932730  | rs4081552  | 0.67                | 6   | 31461668   | A            | G            | 0.31 |                 | <i>HLA-C,HLA-DQB1,MICB</i> | 1.01E-08            |
| rs6932730  | rs16899646 | 0.51                | 6   | 31524899   | G            | C            | 0.15 |                 | <i>HCG4</i>                | 1.16E-07            |
| rs9865818  | rs2030516  | 0.85                | 3   | 189584433  | T            | C            | 0.43 | <i>LPP</i>      | <i>BCL6</i>                | 5.17E-09            |
| rs9865818  | rs9864529  | 0.79                | 3   | 189587750  | G            | A            | 0.45 | <i>LPP</i>      | <i>BCL6</i>                | 5.22E-10            |
| rs9865818  | rs7640550  | 0.79                | 3   | 189562942  | T            | C            | 0.46 | <i>LPP</i>      | <i>BCL6</i>                | 5.51E-09            |
| rs9865818  | rs2030520  | 0.75                | 3   | 189602276  | C            | T            | 0.45 | <i>LPP</i>      | <i>BCL6,SDSL</i>           | 1.12E-09            |
| rs9865818  | rs6780858  | 0.72                | 3   | 189614804  | G            | A            | 0.47 | <i>LPP</i>      | <i>BCL6</i>                | 2.09E-06            |
| rs9865818  | rs13079741 | 0.68                | 3   | 189584555  | G            | C            | 0.49 | <i>LPP</i>      | <i>BCL6</i>                | 1.56E-06            |
| rs9865818  | rs1035766  | 0.51                | 3   | 189603434  | A            | G            | 0.46 | <i>LPP</i>      | <i>BCL6</i>                | 3.10E-07            |
| rs9865818  | rs1035765  | 0.51                | 3   | 189603477  | T            | A            | 0.46 | <i>LPP</i>      | <i>BCL6</i>                | 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    | <i>IL1RL2</i> (+2.7kb)  |                        | HMEC, NHEK             | 13 cell types        |
| rs3771175 | rs10189629 | 0.83                | 2   | 102245896  | A            | C            | 0.152 | Near-gene    | <i>IL1RL2</i> (+23.7kb) |                        |                        | 13 cell types        |
| rs3771175 | rs11690644 | 0.94                | 2   | 102280646  | G            | A            | 0.140 | Near-gene    | <i>IL1RL1</i> (-13.7kb) |                        |                        | HCFaa,HMEC           |
| rs3771175 | rs950881   | 0.98                | 2   | 102298944  | T            | G            | 0.143 | Intron       | <i>IL1RL1</i>           |                        | Huvec, NHEK            | 5 cell types         |
| rs3771175 | rs3771180  | 0.99                | 2   | 102320049  | T            | G            | 0.144 | Intron       | <i>IL1RL1</i>           |                        | HMEC, Huvec, NHEK      | 28 cell types        |
| rs3771175 | rs72823646 | 0.99                | 2   | 102320645  | A            | G            | 0.144 | Intron       | <i>IL1RL1</i>           |                        | Huvec, NHEK            | 7 cell types         |
| rs3771175 | rs13431828 | 0.99                | 2   | 102321085  | T            | C            | 0.144 | UTR-5        | <i>IL1RL1</i>           |                        | Huvec, NHEK            | 11 cell types        |
| rs3771175 | rs13408569 | 0.99                | 2   | 102321488  | C            | G            | 0.144 | Intron       | <i>IL1RL1</i>           |                        | Huvec                  | HCM                  |
| rs3771175 | rs13408661 | 0.99                | 2   | 102321514  | A            | G            | 0.144 | Intron       | <i>IL1RL1</i>           |                        | Huvec                  | HCM                  |
| rs3771175 | rs10173081 | 0.99                | 2   | 102323780  | T            | C            | 0.144 | Intron       | <i>IL1RL1</i>           |                        |                        | 5 cell types         |
| rs3771175 | rs3771175  | 1.00                | 2   | 102326642  | A            | T            | 0.146 | UTR-3,intron | <i>IL1RL1</i>           |                        |                        | HCM,NB4              |
| rs3771175 | rs10185897 | 0.89                | 2   | 102333222  | A            | C            | 0.134 | Intron       | <i>IL1RL1</i>           |                        |                        | HFF-Myc,NB4          |
| rs3771175 | rs56179005 | 0.97                | 2   | 102340760  | A            | G            | 0.144 | Near-gene    | <i>IL18R1</i> (-4.8kb)  | GM12878                |                        | GM06990,GM12878, Th1 |
| rs3771175 | rs72823669 | 0.97                | 2   | 102348465  | T            | G            | 0.144 | Intron       | <i>IL18R1</i>           |                        | GM12878                |                      |
| rs3771175 | rs72823677 | 0.93                | 2   | 102363483  | T            | C            | 0.147 | Intron       | <i>IL18R1</i>           |                        |                        | HAEPiC               |
| rs9865818 | rs9842232  | 0.88                | 3   | 189562857  | G            | C            | 0.436 | Intron       | <i>LPP</i>              |                        | Huvec                  | PANC-1               |
| rs9865818 | rs9864554  | 0.86                | 3   | 189567376  | T            | G            | 0.429 | Intron       | <i>LPP</i>              |                        | Huvec                  |                      |
| rs9865818 | rs9851967  | 0.87                | 3   | 189570322  | T            | C            | 0.434 | Intron       | <i>LPP</i>              |                        | Huvec                  | Gliobla,HRGEC,WI-38  |
| rs9865818 | rs11715549 | 0.87                | 3   | 189570812  | G            | C            | 0.434 | Intron       | <i>LPP</i>              |                        |                        | 8 cell types         |
| rs9865818 | rs11709294 | 0.85                | 3   | 189580729  | A            | T            | 0.429 | Intron       | <i>LPP</i>              |                        | HepG2                  |                      |
| rs9865818 | rs2030516  | 0.85                | 3   | 189584433  | T            | C            | 0.429 | Intron       | <i>LPP</i>              |                        |                        | HRCEpiC,HRE,RPTEC    |
| rs9865818 | rs4686955  | 0.85                | 3   | 189589073  | G            | A            | 0.429 | Intron       | <i>LPP</i>              |                        | HMEC, NHEK             |                      |
| rs9865818 | rs56046601 | 0.85                | 3   | 189591336  | C            | G            | 0.429 | Intron       | <i>LPP</i>              |                        | HMEC, NHEK             | 11 cell types        |
| rs9865818 | rs60946162 | 0.83                | 3   | 189616030  | T            | C            | 0.437 | Intron       | <i>LPP</i>              |                        |                        | HA-h,HCFaa,          |

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

|           |            |      |    |           |   |   |       |           |                              |                      |                |                                 |
|-----------|------------|------|----|-----------|---|---|-------|-----------|------------------------------|----------------------|----------------|---------------------------------|
| rs6932730 | rs6930344  | 1.00 | 6  | 31475968  | A | C | 0.235 | Near-gene | <i>MICA</i> (-3.4kb)         | K562<br>8 cell types | NHLF           | 43 cell types                   |
| rs6932730 | rs6937174  | 1.00 | 6  | 31477164  | A | G | 0.235 | Near-gene | <i>MICA</i> (-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,<br>Huvec |                                 |
| rs4410871 | rs4410871  | 1.00 | 8  | 128884211 | T | C | 0.306 |           |                              | HMEC                 | Huvec,<br>NHEK | 23 cell types                   |
| rs2155219 | rs61893460 | 0.85 | 11 | 75968802  | A | G | 0.440 | Near-gene | <i>C11orf30</i><br>(+28.6kb) |                      | Huvec          |                                 |
| rs2155219 | rs2155219  | 1.00 | 11 | 75976842  | T | G | 0.483 | Near-gene | <i>C11orf30</i><br>(+36.6kb) |                      | Huvec          | Stellate                        |
| rs2155219 | rs11236797 | 0.85 | 11 | 75977297  | A | C | 0.441 | Near-gene | <i>C11orf30</i><br>(+37.1kb) |                      | Huvec          | 47 cell types                   |
| rs1059513 | rs1059513  | 1.00 | 12 | 55775976  | C | T | 0.105 | UTR-3     | <i>STAT6</i>                 |                      | HMEC,<br>NHEK  | Hepatocytes,HMEC,<br>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    | <i>KIAA1109</i> |                   |
| rs17616434 | rs4833095     | 0.95                   | 4   | 38476105   | C            | T            | 0.2402 | Missense | <i>TLR1</i>     | N>S               |
| rs17616434 | chr4:38798935 | 0.94                   | 4   | 38475330   | T            | C            | 0.2402 | Synon    | <i>TLR1</i>     |                   |
| rs6932730  | rs1063630     | 0.83                   | 6   | 31486337   | G            | T            | 0.2126 | Missense | <i>MICA</i>     | W>G               |
| rs6932730  | rs61738275    | 0.83                   | 6   | 31488177   | T            | C            | 0.2126 | Missense | <i>MICA</i>     | 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      | <b>0.53</b> | 1.00        |           |             |               |
| rs2416257  | 0.01          | 0.00       | 0.03      | 0.28        | 0.12        | 1.00      |             |               |
| rs1438673  | 0.00          | 0.01       | 0.03      | <b>0.78</b> | 0.06        | 0.22      | 1.00        |               |
| rs6594499  | 0.00          | 0.00       | 0.02      | <b>0.77</b> | <b>0.56</b> | 0.22      | <b>0.98</b> | 1.00          |

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

| Database  | Gene Set  | Gene set size | Nominal GSEA <i>P</i> 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  | <b>2e-04</b>             | 2                                 | 10                                |
| KEGG      | KEGG_ALLOGRAFT_REJECTION                          | 27            | 9.9e-07  | <b>2e-04</b>             | 1                                 | 10                                |
| KEGG      | KEGG_ASTHMA                                       | 20            | 3.4e-05  | <b>3e-04</b>             | 1                                 | 7                                 |
| BIOCARTA  | TH1TH2_PATHWAY                                    | 18            | 1.7e-05  | <b>0.0011</b>            | 1                                 | 7                                 |
| Ingenuity | PTEN.Signaling                                    | 24            | 2e-04  | <b>0.0017</b>            | 1                                 | 7                                 |
| Ingenuity | Fc.Epsilon.RI.Signaling                           | 17            | 0.000108   | <b>0.0022</b>            | 1                                 | 6                                 |
| BIOCARTA  | ASBCELL_PATHWAY                                   | 11            | 1e-04  | <b>0.0023</b>            | 1                                 | 5                                 |
| Ingenuity | Neuregulin.Signaling                              | 26            | 1e-04  | <b>0.0025333</b>         | 1                                 | 7                                 |
| KEGG      | KEGG_GRAFT_VERSUS_HOST_DISEASE                    | 29            | 4e-04  | <b>0.006975</b>          | 1                                 | 7                                 |
| Ingenuity | Ephrin.Receptor.Signaling                         | 36            | 3e-04  | <b>0.007175</b>          | 2                                 | 8                                 |
| Ingenuity | IGF-1.Signaling                                   | 18            | 0.0012   | <b>0.00864</b>           | 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_CARBOON_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  | <i>HLA-DQA1</i> | 4.207502E-09 | -0.1471 | rs6906021  | 1.284e-08   | Top-locus  |
| KEGG                  | KEGG_AUTOIMMUNE_THYROID_DISEASE  | <i>HLA-DRB1</i> | 5.231583E-09 | -0.1471 | rs6906021  | 1.284e-08   | Top-locus  |
| KEGG                  | KEGG_AUTOIMMUNE_THYROID_DISEASE  | <i>IL2</i>      | 1.900989E-05 | -0.1287 | rs17454584 | 9.468e-06   | Top-locus  |
| KEGG                  | KEGG_AUTOIMMUNE_THYROID_DISEASE  | <i>HLA-DQB1</i> | 6.043204E-05 | -0.1471 | rs6906021  | 1.284e-08   | Top-locus  |
| KEGG                  | KEGG_AUTOIMMUNE_THYROID_DISEASE  | <i>HLA-DQA2</i> | 1.578755E-04 | -0.1471 | rs6906021  | 1.284e-08   | Top-locus  |
| KEGG                  | KEGG_AUTOIMMUNE_THYROID_DISEASE  | <i>IL5</i>      | 6.092586E-04 | 0.1258  | rs17622991 | 6.576e-05   | <b>0.004/yes</b>   |
| KEGG                  | KEGG_AUTOIMMUNE_THYROID_DISEASE  | <i>IL4</i>      | 9.084372E-04 | 0.1521  | rs734244   | 5.518e-05   | 0.14/yes   |
| KEGG                  | KEGG_AUTOIMMUNE_THYROID_DISEASE  | <i>HLA-DRB5</i> | 1.536889E-03 | 0.114   | rs9272535  | 8.364e-05   | Top-locus  |
| KEGG                  | KEGG_AUTOIMMUNE_THYROID_DISEASE  | <i>HLA-B</i>    | 2.059049E-03 | 0.1633  | rs6932730  | 7.944e-07   | Top-locus  |
| KEGG                  | KEGG_AUTOIMMUNE_THYROID_DISEASE  | <i>FASLG</i>    | 3.988489E-03 | -0.1324 | rs1159378  | 0.00014     | 0.56/NA  |
| KEGG                  | KEGG_AUTOIMMUNE_THYROID_DISEASE  | <i>CD86</i>     | 1.129385E-02 | 0.12    | rs1920291  | 0.000252    | <b>0.01/yes</b>  |
| KEGG                  | KEGG_AUTOIMMUNE_THYROID_DISEASE  | <i>CD40</i>     | 1.161140E-02 | -0.1156 | rs12624433 | 0.0001557   | 0.28/yes   |
| KEGG                  | KEGG_AUTOIMMUNE_THYROID_DISEASE  | <i>TG</i>       | 4.224887E-02 | -0.112  | rs988068   | 0.0001416   | 0.94/NA  |
| Non-significant genes | <i>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</i> |                 |              |         |            |             |  |
| KEGG                  | KEGG_ALLOGRAFT_REJECTION   | <i>HLA-DQA1</i> | 4.207502E-09 | -0.1471 | rs6906021  | 1.284e-08   | Top-locus  |
| KEGG                  | KEGG_ALLOGRAFT_REJECTION   | <i>HLA-DRB1</i> | 5.231583E-09 | -0.1471 | rs6906021  | 1.284e-08   | Top-locus  |
| KEGG                  | KEGG_ALLOGRAFT_REJECTION   | <i>IL2</i>      | 1.900989E-05 | -0.1287 | rs17454584 | 9.468e-06   | Top-locus  |
| KEGG                  | KEGG_ALLOGRAFT_REJECTION   | <i>HLA-DQB1</i> | 6.043204E-05 | -0.1471 | rs6906021  | 1.284e-08   | Top-locus  |
| KEGG                  | KEGG_ALLOGRAFT_REJECTION   | <i>HLA-DQA2</i> | 1.578755E-04 | -0.1471 | rs6906021  | 1.284e-08   | Top-locus  |
| KEGG                  | KEGG_ALLOGRAFT_REJECTION   | <i>IL5</i>      | 6.092586E-04 | 0.1258  | rs17622991 | 6.576e-05   | <b>0.004/yes</b>   |
| KEGG                  | KEGG_ALLOGRAFT_REJECTION   | <i>IL4</i>      | 9.084372E-04 | 0.1521  | rs734244   | 5.518e-05   | 0.14/yes   |
| KEGG                  | KEGG_ALLOGRAFT_REJECTION   | <i>HLA-DRB5</i> | 1.536889E-03 | 0.114   | rs9272535  | 8.364e-05   | Top-locus  |
| KEGG                  | KEGG_ALLOGRAFT_REJECTION   | <i>HLA-B</i>    | 2.059049E-03 | 0.1633  | rs6932730  | 7.944e-07   | Top-locus  |
| KEGG                  | KEGG_ALLOGRAFT_REJECTION   | <i>TNF</i>      | 3.972224E-03 | -0.1748 | rs4947324  | 9.074e-06   | Top-locus  |
| KEGG                  | KEGG_ALLOGRAFT_REJECTION   | <i>FASLG</i>    | 3.988489E-03 | -0.1324 | rs1159378  | 0.00014     | 0.56/NA  |
| KEGG                  | KEGG_ALLOGRAFT_REJECTION   | <i>CD86</i>     | 1.129385E-02 | 0.12    | rs1920291  | 0.000252    | <b>0.01/yes</b>  |
| KEGG                  | KEGG_ALLOGRAFT_REJECTION   | <i>CD40</i>     | 1.161140E-02 | -0.1156 | rs12624433 | 0.0001557   | 0.28/yes   |
| Non-significant genes | <i>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</i>   |                 |              |         |            |             |  |
| KEGG                  | KEGG_ASTHMA  | <i>HLA-DQA1</i> | 4.207502E-09 | -0.1471 | rs6906021  | 1.284e-08   | Top-locus  |
| KEGG                  | KEGG_ASTHMA  | <i>HLA-DRB1</i> | 5.231583E-09 | -0.1471 | rs6906021  | 1.284e-08   | Top-locus  |
| KEGG                  | KEGG_ASTHMA  | <i>HLA-DQB1</i> | 6.043204E-05 | -0.1471 | rs6906021  | 1.284e-08   | Top-locus  |
| KEGG                  | KEGG_ASTHMA  | <i>HLA-DQA2</i> | 1.578755E-04 | -0.1471 | rs6906021  | 1.284e-08   | Top-locus  |
| KEGG                  | KEGG_ASTHMA  | <i>IL5</i>      | 6.092586E-04 | 0.1258  | rs17622991 | 6.576e-05   | <b>0.004/yes</b>   |
| KEGG                  | KEGG_ASTHMA  | <i>IL13</i>     | 6.799815E-04 | 0.1521  | rs734244   | 5.518e-05   | 0.14/yes   |
| KEGG                  | KEGG_ASTHMA  | <i>IL4</i>      | 9.084372E-04 | 0.1521  | rs734244   | 5.518e-05   | 0.14/yes   |
| KEGG                  | KEGG_ASTHMA  | <i>HLA-DRB5</i> | 1.536889E-03 | 0.114   | rs9272535  | 8.364e-05   | Top-locus  |
| KEGG                  | KEGG_ASTHMA  | <i>TNF</i>      | 3.972224E-03 | -0.1748 | rs4947324  | 9.074e-06   | Top-locus  |
| KEGG                  | KEGG_ASTHMA  | <i>FCER1A</i>   | 9.093377E-03 | 0.2436  | rs12140357 | 0.0002424   | 0.07/yes   |
| KEGG                  | KEGG_ASTHMA  | <i>CD40</i>     | 1.161140E-02 | -0.1156 | rs12624433 | 0.0001557   | 0.28/yes   |
| Non-significant genes | <i>HLA-DOB, HLA-DRA, HLA-DMB, RNASE3, HLA-DMA, FCER1G, CCL11, EPX, HLA-DPA1, HLA-DOA, HLA-DPB1, PRG2, IL3, MS4A2, IL10, IL9</i>  |                 |              |         |            |             |  |

|                       |   |                 |              |         |            |           |                 |
|-----------------------|---|-----------------|--------------|---------|------------|-----------|-----------------|
| BIOCARTA              | TH1TH2_PATHWAY  | <i>HLA-DRB1</i> | 5.231583E-09 | -0.1471 | rs6906021  | 1.284e-08 | Top-locus       |
| BIOCARTA              | TH1TH2_PATHWAY  | <i>IL2</i>      | 1.900989E-05 | -0.1287 | rs17454584 | 9.468e-06 | Top-locus       |
| BIOCARTA              | TH1TH2_PATHWAY  | <i>IL18R1</i>   | 5.490214E-04 | 0.1122  | rs6759479  | 8.267e-06 | Top-locus       |
| BIOCARTA              | TH1TH2_PATHWAY  | <i>IL4</i>      | 9.084372E-04 | 0.1521  | rs734244   | 5.518e-05 | 0.14/yes        |
| BIOCARTA              | TH1TH2_PATHWAY  | <i>IL4R</i>     | 5.072796E-03 | -0.1529 | rs2234898  | 0.0001067 | 0.17/yes        |
| BIOCARTA              | TH1TH2_PATHWAY  | <i>CD86</i>     | 1.129385E-02 | 0.12    | rs1920291  | 0.000252  | <b>0.01/yes</b> |
| BIOCARTA              | TH1TH2_PATHWAY  | <i>CD40</i>     | 1.161140E-02 | -0.1156 | rs12624433 | 0.0001557 | 0.28/yes        |
| Non-significant genes | <i>IL12A, HLA-DRA, IL2RA, IFNG, CD28, IFNGR2, IL18, IFNGR1, IL12RB2, IL12RB1, IL12B</i> |                 |              |         |            |           |                 |

|                       |  |              |              |         |            |           |                  |
|-----------------------|--|--------------|--------------|---------|------------|-----------|------------------|
| Ingenuity             | PTEN.Signaling   | <i>FASLG</i> | 3.988489E-03 | -0.1324 | rs1159378  | 0.00014   | 0.56/NA          |
| Ingenuity             | PTEN.Signaling   | <i>BAD</i>   | 4.047106E-03 | 0.0942  | rs10897487 | 0.000247  | 0.11/yes         |
| Ingenuity             | PTEN.Signaling   | <i>CCND1</i> | 1.275392E-02 | -0.119  | rs7109260  | 0.0002272 | Missing          |
| Ingenuity             | PTEN.Signaling   | <i>SHC1</i>  | 2.192242E-02 | 0.1072  | rs12023499 | 0.0006063 | 0.33/yes         |
| Ingenuity             | PTEN.Signaling   | <i>PTK2</i>  | 2.364044E-02 | -0.098  | rs10108278 | 0.0002812 | 0.72/NA          |
| Ingenuity             | PTEN.Signaling   | <i>PTEN</i>  | 2.517105E-02 | 0.1088  | rs10887758 | 0.000602  | 0.09/yes         |
| Ingenuity             | PTEN.Signaling   | <i>PRKCZ</i> | 2.546894E-02 | -0.1007 | rs3107156  | 0.0006142 | <b>0.047/yes</b> |
| Non-significant genes | <i>BCAR1, PIK3R5, CASP3, PIK3CG, BCL2L11, BCL2, CDKN1B, RAF1, PDPK1, CBL, CASP9, ILK, YWHAH, BCL2L1, CDKN1A, LOC643751, GRB2</i> |              |              |         |            |           |                  |

|                       |  |               |              |         |            |           |                  |
|-----------------------|--|---------------|--------------|---------|------------|-----------|------------------|
| Ingenuity             | Fc.Epsilon.RI.Signaling  | <i>IL5</i>    | 6.092586E-04 | 0.1258  | rs17622991 | 6.576e-05 | <b>0.004/yes</b> |
| Ingenuity             | Fc.Epsilon.RI.Signaling  | <i>IL13</i>   | 6.799815E-04 | 0.1521  | rs734244   | 5.518e-05 | <b>0.03/yes</b>  |
| Ingenuity             | Fc.Epsilon.RI.Signaling  | <i>IL4</i>    | 9.084372E-04 | 0.1521  | rs734244   | 5.518e-05 | 0.14/yes         |
| Ingenuity             | Fc.Epsilon.RI.Signaling  | <i>TNF</i>    | 3.972224E-03 | -0.1748 | rs4947324  | 9.074e-06 | Top-locus        |
| Ingenuity             | Fc.Epsilon.RI.Signaling  | <i>FCER1A</i> | 9.093377E-03 | 0.2436  | rs12140357 | 0.0002424 | 0.23/yes         |
| Ingenuity             | Fc.Epsilon.RI.Signaling  | <i>PTPN11</i> | 1.247699E-02 | -0.0891 | rs11066320 | 0.0005513 | <b>0.01/yes</b>  |
| Ingenuity             | Fc.Epsilon.RI.Signaling  | <i>FYN</i>    | 1.388087E-02 | -0.1684 | rs9487769  | 9.728e-05 | 0.47/no          |
| Non-significant genes | <i>LYN, FCER1G, RAF1, LCP2, PDPK1, SYK, IL3, CSF2, GRAP2, LAT, MS4A2, GRB2</i> |               |              |         |            |           |                  |

|                       |  |                 |              |         |            |           |           |
|-----------------------|--|-----------------|--------------|---------|------------|-----------|-----------|
| BIOCARTA              | ASBCELL_PATHWAY                            | <i>HLA-DRB1</i> | 5.231583E-09 | -0.1471 | rs6906021  | 1.284e-08 | Top-locus |
| BIOCARTA              | ASBCELL_PATHWAY                            | <i>IL2</i>      | 1.900989E-05 | -0.1287 | rs17454584 | 9.468e-06 | Top-locus |
| BIOCARTA              | ASBCELL_PATHWAY                            | <i>IL4</i>      | 9.084372E-04 | 0.1521  | rs734244   | 5.518e-05 | 0.14/yes  |
| BIOCARTA              | ASBCELL_PATHWAY                            | <i>FASLG</i>    | 3.988489E-03 | -0.1324 | rs1159378  | 0.00014   | Top-locus |
| BIOCARTA              | ASBCELL_PATHWAY                            | <i>CD40</i>     | 1.161140E-02 | -0.1156 | rs12624433 | 0.0001557 | 0.28/yes  |
| Non-significant genes | <i>HLA-DRA, CD4, CD80, CD28, FAS, IL10</i> |                 |              |         |            |           |           |

|                       |  |               |              |         |            |           |                 |
|-----------------------|--|---------------|--------------|---------|------------|-----------|-----------------|
| Ingenuity             | Neuregulin.Signaling   | <i>MYC</i>    | 5.705052E-05 | -0.1246 | rs4326353  | 4.374e-06 | Top-locus       |
| Ingenuity             | Neuregulin.Signaling   | <i>ERBB3</i>  | 3.321814E-04 | 0.1068  | rs2271189  | 4.938e-05 | 0.79/NA         |
| Ingenuity             | Neuregulin.Signaling   | <i>BAD</i>    | 4.047106E-03 | 0.0942  | rs10897487 | 0.000247  | 0.10/yes        |
| Ingenuity             | Neuregulin.Signaling   | <i>PTPN11</i> | 1.247699E-02 | -0.0891 | rs11066320 | 0.0005513 | <b>0.01/yes</b> |
| Ingenuity             | Neuregulin.Signaling   | <i>SHC1</i>   | 2.192242E-02 | 0.1072  | rs12023499 | 0.0006063 | 0.33/yes        |
| Ingenuity             | Neuregulin.Signaling   | <i>PTEN</i>   | 2.517105E-02 | 0.1088  | rs10887758 | 0.000602  | 0.09/yes        |
| Ingenuity             | Neuregulin.Signaling   | <i>GRB7</i>   | 3.400819E-02 | -0.1122 | rs2313430  | 0.001369  | Missing         |
| Non-significant genes | <i>RNF41, MATK, EGFR, CDK5, ADAM17, PICK1, CDKN1B, CDK5R1, FRAP1, RAF1, ERBB2, PDPK1, RPS6, DLG4, GRB2, SRC, ERBB4, PSEN1, ERRF1</i> |               |              |         |            |           |                 |

|      |                                |                 |              |         |            |           |           |
|------|--------------------------------|-----------------|--------------|---------|------------|-----------|-----------|
| KEGG | KEGG_GRAFT_VERSUS_HOST_DISEASE | <i>HLA-DQA1</i> | 4.207502E-09 | -0.1471 | rs6906021  | 1.284e-08 | Top-locus |
| KEGG | KEGG_GRAFT_VERSUS_HOST_DISEASE | <i>HLA-DRB1</i> | 5.231583E-09 | -0.1471 | rs6906021  | 1.284e-08 | Top-locus |
| KEGG | KEGG_GRAFT_VERSUS_HOST_DISEASE | <i>IL2</i>      | 1.900989E-05 | -0.1287 | rs17454584 | 9.468e-06 | Top-locus |
| KEGG | KEGG_GRAFT_VERSUS_HOST_DISEASE | <i>HLA-DQB1</i> | 6.043204E-05 | -0.1471 | rs6906021  | 1.284e-08 | Top-locus |

|      |                                |                 |              |         |           |           |                 |
|------|--------------------------------|-----------------|--------------|---------|-----------|-----------|-----------------|
| KEGG | KEGG_GRAFT_VERSUS_HOST_DISEASE | <i>HLA-DQA2</i> | 1.578755E-04 | -0.1471 | rs6906021 | 1.284e-08 | Top-locus       |
| KEGG | KEGG_GRAFT_VERSUS_HOST_DISEASE | <i>HLA-DRB5</i> | 1.536889E-03 | 0.114   | rs9272535 | 8.364e-05 | Top-locus       |
| KEGG | KEGG_GRAFT_VERSUS_HOST_DISEASE | <i>HLA-B</i>    | 2.059049E-03 | 0.1633  | rs6932730 | 7.944e-07 | Top-locus       |
| KEGG | KEGG_GRAFT_VERSUS_HOST_DISEASE | <i>TNF</i>      | 3.972224E-03 | -0.1748 | rs4947324 | 9.074e-06 | Top-locus       |
| KEGG | KEGG_GRAFT_VERSUS_HOST_DISEASE | <i>FASLG</i>    | 3.988489E-03 | -0.1324 | rs1159378 | 0.00014   | 0.56/NA         |
| KEGG | KEGG_GRAFT_VERSUS_HOST_DISEASE | <i>CD86</i>     | 1.129385E-02 | 0.12    | rs1920291 | 0.000252  | <b>0.01/yes</b> |

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 | <i>SH2D3C</i>   | 4.616593E-03 | -0.1053 | rs7865146  | 0.0001473 | Missing             |
| Ingenuity | Ephrin.Receptor.Signaling | <i>ARHGEF15</i> | 8.832307E-03 | -0.1071 | rs4792722  | 0.0002665 | 0.40/yes            |
| Ingenuity | Ephrin.Receptor.Signaling | <i>PTPN11</i>   | 1.247699E-02 | -0.0891 | rs11066320 | 0.0005513 | <b>5.5 E-04/yes</b> |
| Ingenuity | Ephrin.Receptor.Signaling | <i>FYN</i>      | 1.388087E-02 | -0.1684 | rs9487769  | 9.728e-05 | 0.90/NA             |
| Ingenuity | Ephrin.Receptor.Signaling | <i>ACP1</i>     | 2.003080E-02 | -0.1373 | rs385272   | 0.0003645 | 0.81/NA             |
| Ingenuity | Ephrin.Receptor.Signaling | <i>PXN</i>      | 2.172863E-02 | 0.153   | rs11611311 | 0.000642  | 0.70/NA             |
| Ingenuity | Ephrin.Receptor.Signaling | <i>SHC1</i>     | 2.192242E-02 | 0.1072  | rs12023499 | 0.0006063 | 0.33/yes            |
| Ingenuity | Ephrin.Receptor.Signaling | <i>PTK2</i>     | 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 | <i>BAD</i>    | 4.047106E-03 | 0.0942  | rs10897487 | 0.000247  | 0.11/yes            |
| Ingenuity | IGF-1.Signaling | <i>PTPN11</i> | 1.247699E-02 | -0.0891 | rs11066320 | 0.0005513 | <b>5.5 E-04/yes</b> |
| Ingenuity | IGF-1.Signaling | <i>PXN</i>    | 2.172863E-02 | 0.153   | rs11611311 | 0.000642  | 0.70/NA             |
| Ingenuity | IGF-1.Signaling | <i>SHC1</i>   | 2.192242E-02 | 0.1072  | rs12023499 | 0.0006063 | 0.33/yes            |
| Ingenuity | IGF-1.Signaling | <i>PTK2</i>   | 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.

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

<sup>†</sup> 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.

| Region  | SNP        | Nearest gene         | Effect allele | Allergic sensitization |                      | Eczema           |                 | Same direction of effect |
|---------|------------|----------------------|---------------|------------------------|----------------------|------------------|-----------------|--------------------------|
|         |            |                      |               | Current meta-analysis  |                      | OR               | P value         |                          |
| 11q13.5 | rs2155219  | <i>C11orf30</i>      | t             | 1.18 (1.13-1.22)       | 1.4E-18              | 1.08 (1.03-1.14) | <b>7.0E-04*</b> | yes                      |
| 12q13.3 | rs1059513  | <i>STAT6</i>         | t             | 1.30 (1.21-1.39)       | 1.0E-14              | 1.14 (1.05-1.25) | <b>0.001*</b>   | yes                      |
| 5q22.1  | rs10056340 | <i>SLC25A46</i>      | t             | 0.83 (0.78-0.87)       | 5.2E-14              | 0.96 (0.90-1.02) | 0.16            | yes                      |
| 6p21.32 | rs6906021  | <i>HLADQB1</i>       | t             | 0.87 (0.83-0.90)       | 2.2E-12              | 0.97 (0.92-1.02) | 0.18            | yes                      |
| 2q12.1  | rs3771175  | <i>IL1RL1/IL18R1</i> | a             | 0.83 (0.78-0.88)       | 4.9E-11              | 0.93 (0.86-1.01) | 0.08            | yes                      |
| 4p14    | rs17616434 | <i>TLR1/6/10</i>     | t             | 1.23 (1.18-1.29)       | 5.2E-11 <sup>+</sup> | 1.02 (0.97-1.08) | 0.42            | yes                      |
| 3q28    | rs9865818  | <i>LPP</i>           | a             | 0.89 (0.86-0.92)       | 2.7E-10              | 0.97 (0.92-1.02) | 0.20            | yes                      |
| 8q24.21 | rs4410871  | <i>MYC/PVT1</i>      | t             | 1.14 (1.09-1.19)       | 5.4E-10              | 1.02 (0.97-1.07) | 0.44            | yes                      |
| 4q27    | rs17454584 | <i>IL2/ADAD1</i>     | a             | 0.87 (0.83-0.91)       | 5.5E-10              | 0.93 (0.88-0.98) | 0.01            | yes                      |
| 6p21.33 | rs6932730  | <i>HLA-B/MICA</i>    | 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 ( $P < 0.005$ )

<sup>+</sup> 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**

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

\* 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**

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

\* 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 Engl J Med* 2010; 363: 1211-21.

**c) Eosinophil numbers**

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

\* 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**

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

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

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

**b) Asthma**

| Position | Gene            | Ref | SNP        | Effect allele | Asthma  | Sensitization           |                 |
|----------|-----------------|-----|------------|---------------|---------|-------------------------|-----------------|
|          |                 |     |            |               | P-value | (current meta-analysis) |                 |
|          |                 |     |            |               |         | OR (95% CI)             | P value         |
| 1q21.3   | <i>IL6R</i>     | 1   | rs4129267  | T             | 2.3E-08 | 1.08 (1.02-1.14)        | 0.01            |
| 1q31.3   | <i>DENND1B</i>  | 2   | rs2786098  | T             | 9.3E-11 | 0.96 (0.90-1.02)        | 0.22            |
| 2q12.1   | <i>IL1RL1</i>   | 3   | rs3771180  | T             | 1.5E-15 | 1.17 (1.09-1.25)        | <b>2.1E-05*</b> |
| -        | <i>IL1RL1</i>   | 4   | rs1420101  | T             | 5.5E-12 | 1.11 (1.05-1.16)        | <b>9.8E-05</b>  |
| -        | <i>IL18R1</i>   | 5   | rs3771166  | A             | 3.4E-09 | 0.89 (0.85-0.94)        | <b>1.5E-05</b>  |
| 5        | <i>PDE4D</i>    | 6   | rs1588265  | G             | 2.5E-08 | 1.00 (0.95-1.06)        | 0.97            |
| 5        | <i>TSLP</i>     | 3   | rs1837253  | T             | 1.0E-14 | 1.05 (0.98-1.11)        | 0.14            |
| 6p21.3   | <i>HLA-DQB1</i> | 5   | rs9273349  | T             | 7.0E-14 | 0.93 (0.87-1.00)        | 0.04*           |
| 9p24.1   | <i>IL33</i>     | 3   | rs2381416  | A             | 1.7E-12 | 1.02 (0.97-1.08)        | 0.43            |
| -        | <i>IL33</i>     | 5   | rs1342326  | C             | 9.2E-10 | 1.01 (0.94-1.08)        | 0.85            |
| 11q13.5  | <i>C11ORF30</i> | 1   | rs7130588  | G             | 1.8E-08 | 1.18 (1.12-1.25)        | <b>3.7E-10*</b> |
| 15q22.3  | <i>SMAD3</i>    | 5   | rs744910   | A             | 3.9E-09 | 0.95 (0.90-1.00)        | 0.03            |
| 17q12-21 | <i>GSDM</i>     | 3   | rs11078927 | T             | 2.2E-16 | 1.04 (0.99-1.10)        | 0.12            |
| -        | <i>GSDM1</i>    | 5   | rs3894194  | A             | 4.6E-09 | 1.06 (1.01-1.11)        | 0.02            |
| -        | <i>GSDMB</i>    | 5   | rs2305480  | A             | 9.6E-08 | 0.96 (0.91-1.02)        | 0.16            |
| 22q12.3  | <i>IL2RB</i>    | 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 et 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 Engl J Med 2010; 363: 1211-21.

Reference no. 6: Himes et al. Am J Hum Gen 2009; 84: 581-93.

| c) Eczema |                       |     |           |               | Eczema  | Sensitization<br>(current meta-analysis) |                 |
|-----------|-----------------------|-----|-----------|---------------|---------|--|-----------------|
| Position  | Gene                  | Ref | SNP       | Effect allele | P-value | OR (95% CI)                              | P value         |
| 1q21      | <i>EDC-region/FLG</i> | 1   | rs6661961 | T             | 1.2E-09 | 1.07 (1.02-1.13)                         | 0.009           |
| -         | <i>EDC-region/FLG</i> | 2   | rs9050    | A             | 1.9E-08 | 1.10 (0.97-1.25)                         | 0.13            |
| 5         | <i>KIF3A</i>          | 2   | rs2897442 | T             | 7.1E-09 | 0.91 (0.86-0.96)                         | <b>9.8E-04*</b> |
| 11        | <i>OVOL1</i>          | 2   | rs479844  | A             | 1.1E-13 | 0.94 (0.89-0.99)                         | 0.02            |
| 11q13.5   | <i>C11ORF30</i>       | 1   | rs7927894 | T             | 7.6E-10 | 1.20 (1.14-1.27)                         | <b>1.0E-11*</b> |
| 19        | <i>ACTL9</i>          | 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) <sup>1</sup> | Conservative PARF (95% CI) <sup>2</sup> |
|---|------------------------------|--------|--|----------------|--|---|
| <b>Sensitization, specific IgE 0.35 IU/mL</b> | HEALTH2006 replication       | 18-69y | Birch, grass, cat and house dust mite          | 739/2402       | <b>0.71 (0.54,0.83)</b>                  | <b>0.35 (0.17,0.51)</b>                 |
|   | B58C replication             | 44-45y | Cat, mixed grass and house dust mite           | 634/1498       | <b>0.69 (0.48,0.82)</b>                  | <b>0.27 (0.06,0.44)</b>                 |
| <b>Sensitization, specific IgE 3.5 IU/mL</b>  | HEALTH2006 replication       | 18-69y | Birch, grass, cat and house dust mite          | 466/2675       | <b>0.80 (0.64,0.89)</b>                  | <b>0.33 (0.07,0.52)</b>                 |
|   | B58C replication             | 44-45y | Cat, mixed grass and house dust mite           | 289/1843       | <b>0.75 (0.47,0.89)</b>                  | <b>0.41 (0.07,0.63)</b>                 |
| <b>Sensitization SPT 3mm</b>                  | HEALTH2006 replication       | 18-69y | 10 inhalant allergens                          | 659/1502       | <b>0.71 (0.51,0.83)</b>                  | <b>0.29 (0.09,0.46)</b>                 |
|   | ALSPAC discovery+replication | 7.5y   | Grass, house dust mite, cat, egg, peanut, nuts | 804/3181       | <b>0.76 (0.58,0.87)</b>                  | <b>0.41 (0.23,0.55)</b>                 |
| <b>Allergic rhinitis</b>                      | HEALTH2006 replication       | 18-69y | Questionnaire, hayfever current                | 558/2527       | <b>0.64 (0.40,0.79)</b>                  | <b>0.28 (0.04,0.46)</b>                 |
|   | B58C replication             | 42y    | Questionnaire, hayfever ever                   | 529/1853       | <b>0.73 (0.52,0.85)</b>                  | <b>0.48 (0.26,0.60)</b>                 |
|   | ALSPAC discovery+replication | 11y    | Questionnaire, hayfever current                | 902/3773       | <b>0.80 (0.67,0.89)</b>                  | <b>0.26 (0.08,0.41)</b>                 |

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<br>Current meta-analysis |                      |            |                                    | Relationship |                      | GWAS Catalogue        |                |                                   |                                |  |
|---|----------------------|------------|------------------------------------|--------------|----------------------|-----------------------|----------------|-----------------------------------|--------------------------------|--|
| Position  | Nearest Gene         | Index SNP  | Catalogue<br>SNP <i>P</i><br>Value | Distance     | Rsquare /<br>D-prime | GWAS Catalogue<br>SNP | <i>P</i> Value | Disease or Trait                  | Same<br>direction<br>of effect | Reference                                  |
| 2q12.1  | <i>IL1RL1/IL18R1</i> | rs3771175  | 2.0E-05                            | 6593         | 0.96/1               | rs3771180             | 2.00E-15       | Asthma                            | yes                            | Torgerson DG<br>Nat Genet, 2011            |
| 4q27  | <i>IL2/ADAD1</i>     | rs17454584 | 5.4E-05                            | 24070        | 0.65/1               | rs17388568            | 3.00E-06       | Type 1 diabetes                   | yes                            | WTCCC<br>Nature, 2007                      |
| -   | -                    | -          | 5.4E-05                            | 24070        | 0.65/1               | rs17388568            | 6.00E-06       | Type 1 diabetes<br>autoantibodies | yes                            | Plagnol V<br>PLoS Genet, 2011              |
| -   | -                    | -          | 5.4E-05                            | 24070        | 0.65/1               | rs17388568            | 9.00E-07       | Ulcerative colitis                | yes                            | Anderson CA<br>Nat Genet, 2011             |
| 6p21.33   | <i>HLA-B/MICA</i>    | rs6932730  | 5.7E-06                            | 378          | 0.71/1               | rs13437082            | 5.00E-08       | Height                            | no                             | Soranzo N<br>PLoS Genet, 2009              |
| 8q24.21   | <i>MYC/PVT1</i>      | rs4410871  | 1.8E-07                            | 0            | 1.00/1               | rs4410871             | 8.00E-09       | Multiple sclerosis                | no                             | Sawcer S<br>Nature, 2011                   |
| 11q13.5   | <i>C11orf30</i>      | rs2155219  | 1.6E-12                            | 0            | 1.00/1               | rs2155219             | 5.00E-16       | Ulcerative colitis                | yes                            | Anderson CA<br>Nat Genet, 2011             |
| -   | -                    | -          | 1.6E-12                            | 0            | 1.00/1               | rs2155219             | 1.00E-08       | IgE grass sensitization           | yes                            | Ramasamy A<br>J Allergy Clin Immunol, 2011 |
| -   | -                    | -          | 1.6E-12                            | 0            | 1.00/1               | rs2155219             | 4.00E-08       | Allergic rhinitis                 | yes                            | Ramasamy A<br>J Allergy Clin Immunol, 2011 |
| -   | -                    | -          | 9.2E-12                            | 2122         | 0.69/1               | rs7927894             | 1.00E-09       | Crohn's disease                   | yes                            | Barrett JC<br>Nat Genet, 2008              |
| -   | -                    | -          | 9.2E-12                            | 2122         | 0.69/1               | rs7927894             | 8.00E-10       | Atopic dermatitis                 | yes                            | Esparza-Gordillo J<br>Nat Genet, 2009      |
| -   | -                    | -          | 3.3E-10                            | 28511        | 0.66/1               | rs7130588             | 2.00E-08       | Asthma                            | yes                            | Ferreira MA<br>Lancet, 2011                |
| 12q13.3   | <i>STAT6</i>         | rs1059513  | 1.4E-10                            | 0            | 1.00/1               | rs1059513             | 2.00E-12       | IgE levels                        | yes                            | Granada M<br>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,<sup>2</sup> allergic rhinitis,<sup>2</sup> asthma,<sup>3</sup> eczema,<sup>4</sup> ulcerative colitis<sup>5</sup> and Crohn's disease<sup>6</sup> ( $r^2 > 0.66$  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.<sup>7,8</sup> 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)<sup>9</sup>, pediatric eosinophilic esophagitis (rs3806932)<sup>10</sup>, asthma (rs1837253<sup>11,12</sup>, rs1438673<sup>3</sup>) and allergic rhinitis (rs17513503 and rs1898671)<sup>2</sup>. 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.<sup>13</sup>

Variation in human leukocyte antigen (HLA) haplotypes was first linked to ragweed sensitization forty years ago<sup>14</sup> and the major histocompatibility complex (MHC) region became established as a genetic determinant of allergy and asthma well before the era of molecular genetics.<sup>15</sup> 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.<sup>16</sup> By the start of the GWAS era, *HLA-DQ* and *HLA-DR* were among the most widely reported genetic associations for asthma and allergy.<sup>17</sup> Our strongest signal in this region (rs6906021) was also top-SNP in the accompanying paper on self-reported allergy.<sup>1</sup> 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<sup>18</sup> (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,<sup>2</sup> 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,<sup>19</sup> drug hypersensitivity,<sup>20</sup> and psoriasis.<sup>21</sup>

The locus on chromosome 2q tagging *IL1RL1/IL18R1/IL18RAP* is strongly supported by this meta-analysis and the accompanying paper on self-reported allergy.<sup>1</sup> *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,<sup>3,12</sup> and in much lower LD with SNPs found in the largest GWAS on asthma to date.<sup>18</sup> 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.<sup>22</sup> The SNP was associated with expression of *IL18RAP* in white blood cells and whole blood (**Supplementary Table 6**) and with expression of *IL1RL1* in B-cells (**Supplementary Table 7**). LD with rs1420101, a SNP previously reported to be associated with blood eosinophils and asthma is low.<sup>9</sup>

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*, *-10*, *MIR574* and *FAM114A1*. *TLR1*, *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.<sup>23</sup> Rs17616434 tags a haplotype that has previously been associated with asthma and atopy.<sup>24-26</sup> TLR dependent gene expression and cytokine production was altered in individuals with risk variants suggesting that polymorphisms in this region modify specific T cell dependent cytokine expression after stimulation of their respective heterodimers.<sup>26</sup> *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.<sup>27</sup> *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)<sup>28</sup>, celiac disease (CD)<sup>29</sup> and

asthma.<sup>3</sup> 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<sup>30</sup> and serves as a substrate of the protein-tyrosine phosphatase 1B, a regulator of signalling pathways linked to Ras signalling.<sup>31</sup> Also, association analyses of gene expression levels measured in monocytes<sup>32</sup> identified a nearby variant – rs9864529, which is in LD ( $r^2 = 0.73$ ) with rs9865818 – that is a *cis* acting eQTL for *BCL6* ( $P = 5.2 \times 10^{-9}$ ), a gene located 618 kb away. *BCL6* encodes a zinc finger transcriptional repressor that is normally expressed in both B cells and CD4<sup>+</sup> T cells within germinal centers.<sup>33-35</sup> 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.<sup>36</sup> 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<sup>37</sup>, Lupus<sup>38</sup>, Crohn's disease<sup>39</sup>, Ulcerative Colitis<sup>40</sup> and rheumatoid arthritis.<sup>41</sup> However, LD of our top locus rs17454584 is moderate with the SNPs reported in those GWASes (max  $r^2 = 0.586$ ,  $D' = 1$ ). *IL2* and *IL21* are strong candidate genes for atopy in this region. One of the functions of *IL2* produced mainly by CD4<sup>+</sup> and CD8<sup>+</sup> 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<sup>+</sup> T cells, regulates B cell function by affecting antibody isotype balance, proliferation, apoptosis and differentiation into plasma cells.<sup>42</sup> 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*<sup>43</sup> and *IL21*<sup>44</sup> 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 sIgE levels in the B58C. Similarly, in Health2006, the top 20% of risk score identified 27% cases with detectable sIgE, 30% cases with high sIgE, 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.<sup>45</sup> 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.<sup>46</sup> 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<sup>1</sup>. 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<sup>3</sup>. 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 <sup>47</sup> 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 ( $P < 5 \times 10^{-7}$ ) 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 ( $r^2 < 0.30$ ) 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<sup>48, 49</sup> 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 ( $P > 5 \times 10^{-7}$ ) 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,<sup>50</sup> 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)<sup>51</sup> and the Type 1 Diabetes Genetics Consortium (T1DGC).<sup>52</sup> 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<sup>18</sup> 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 Review 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 ( $\geq 3$ mm) 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.<sup>53-55</sup> 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<sup>56</sup> (Phadia AB, Uppsala, Sweden). Samples positive for the Phadiatop screening test ( $\geq 0.35$  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.<sup>57</sup>

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 *pteronysinus* 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.<sup>58</sup> 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<sup>®</sup> 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 Health 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.<sup>59</sup> 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 log<sub>2</sub> 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 (LISApplus) 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.<sup>60</sup>

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.<sup>61</sup> 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 LISApplus and GINIplus studies have been published elsewhere<sup>62</sup> and<sup>63</sup>, 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 LISApplus study Munich with specific 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.<sup>64</sup>

Genome-wide association analysis of allergic sensitization was carried out in SNPTEST V1 ([https://mathgen.stats.ox.ac.uk/genetics\\_software/snptest/snptest.html](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 specific 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 LISApplus study Munich). 387 individuals (321 from the GINIplus study and 66 from the LISApplus study) were analysed using the Affymetrix Human SNP Array 5.0 and 51 individuals from the LISApplus 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<sup>22</sup> 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](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.e. population-based), birth cohort study.<sup>65-69</sup> 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](http://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, Elkhart, IN, USA]). We also measured specific serum IgE to mite, cat, dog, grasses, milk, egg and peanut by ImmunoCAP™ (Phadia, Uppsala, Sweden) in 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 genotyped 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  $> 5.9 \times 10^{-7}$ , minor allele frequency  $> 0.005$ . Genotypes were imputed 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).<sup>70</sup> 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 (*Dermatophagoides pteronyssinus*) 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.<sup>71</sup>

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.<sup>72</sup> 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.<sup>73</sup>

Sensitivity to cat, birch, timothy grass, and to house dust mite (*Dermatophagoides pteronyssinus*) 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.<sup>74</sup>

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 ( $\geq 1$  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 more positive skin test with a diameter of 3 mm or larger. For specific IgE to inhalant allergens, we included 161 cases ( $\geq 0.35$  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 fulfilled 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.<sup>75-77</sup> 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.<sup>78</sup> 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.

### **Collaborating Consortia Members**

#### **AAGC – Australian Asthma Genetics Consortium**

Guy B. Marks<sup>1</sup>, Patrick Danoy<sup>2</sup>, Desiree Mészáros<sup>3</sup>, Catherine Hayden<sup>4</sup>, Anjali K Henders<sup>5</sup>, Brett Chapman<sup>5</sup>, Andrew J. Kemp<sup>6</sup>, Faang Cheah<sup>7</sup>, Melissa C. Southey<sup>8</sup>, Mary Roberts<sup>9</sup>, Euan R. Tovey<sup>1</sup>, Graham Giles<sup>11</sup>, Li P Chung<sup>7</sup>, Paul S Thomas<sup>12</sup>, Ian Feather<sup>13</sup>, Suzanna Temple<sup>7</sup>, John Beilby<sup>14</sup>, Stephen Morrison<sup>15</sup>, David P Johns<sup>3</sup>, Chalermchai Mitrpant<sup>7</sup>, Brad Shelton<sup>7</sup>, Mark Jenkins<sup>2</sup>, Warwick J Britton<sup>16</sup>, Andrew S Kemp<sup>6</sup>, Peter Le Souëf<sup>4</sup>, John L Hopper<sup>17</sup>, Stephen R Leeder<sup>18</sup>, Bill Musk<sup>14</sup>, Nicholas G Martin<sup>5</sup>, Matthew A Brown<sup>2</sup>.

- 1) Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia.
- 2) University of Queensland Diamantina Institute, Princess Alexandra Hospital, Brisbane, Australia.
- 3) Menzies Research Institute, Hobart, Australia.
- 4) School of Paediatrics and Child Health, Princess Margaret Hospital for Children, Perth, Australia.
- 5) The Queensland Institute of Medical Research, Brisbane, Australia.
- 6) The Children's Hospital, Westmead, Sydney, Australia.
- 7) Lung Institute of WA and Centre for Asthma, Allergy and Respiratory Research, University of WA, Perth, Australia.
- 8) Department of Pathology, The University of Melbourne, Melbourne, Australia.
- 9) Department of Respiratory Medicine, Royal Children's Hospital, Parkville, Australia.
- 10) Launceston General Hospital, Launceston, Australia.
- 11) Cancer Epidemiology Centre, The Cancer Council Victoria, Melbourne, Australia.
- 12) Faculty of Medicine, University of New South Wales, Sydney, Australia.
- 13) Gold Coast Hospital, Southport, Australia.
- 14) Busselton Population Medical Research Foundation, Sir Charles Gairdner Hospital, Perth, WA, Australia.

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1) Medical Research Council Causal Analysis in Translational Epidemiology (CAiTE) centre, Bristol, UK

2) Institute of Epidemiology I, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany

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