META-ANALYSIS OF GENOME-WIDE ASSOCIATION STUDIES IDENTIFIES THREE NEW RISK LOCI FOR ATOPIC DERMATITIS

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SUPPLEMENTARY NOTE

Note on nomenclature

The extant nosology of atopic disease is confusing, and terms such as *atopic dermatitis, eczema, atopic eczema, endogenous eczema* and *flexural dermatitis* are frequently used interchangeably in the literature. Recently, a World Allergy Organization (WAO) report suggested the use of *eczema* as preferable to *atopic dermatitis*[1]. However, in this article, we continued to use the term atopic dermatitis, as many studies used for this project were designed prior to the WAO report and because this is the term used in many questionnaires on which the results presented here are based.

STUDY SAMPLE DESCRIPTIONS

Australian Asthma Genetics Consortium (AAGC) replication cohort

As part of the AAGC, we performed a GWAS of asthma in 7,197 unrelated individuals of European ancestry ascertained from the Australian population as described in detail elsewhere {Ferreira, submitted}. For this analysis, we tested 10 SNPs for association with AD status in 3,881 individuals (49% males, mean age 35 years, range 3 to 89), including 269 who reported having had AD at any point in their lifetime diagnosed by a doctor and 3,612 AD-free controls. These individuals participated in one of five studies: QIMR (N=3,132), CAPS (N=53), LIWA (N=474), MESCA (N=64) or TAHS (N=158). The QIMR individuals included in the AAGC analysis are unrelated to those included in the QIMR discovery cohort described below. Genotyping was performed with Illumina 610K or 370K arrays and stringent quality control filters applied as described in Supplementary Table 2. 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 logistic regression in PLINK, with sex and array type included as a covariate. Participants provided informed consent to participate in this study, which was approved by the respective ethics committees.

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 [2] 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. Questionnaire data has been collected regularly, with extensive questions, including those relating to AD. In this study we included data from the following questions, asked when the children were approximately 81, 91, 103 months, 10, 13 and 14 years [possible answers]:

1. Has your child in the past 12 months had eczema? [yes, saw a Dr; Yes, but did not see a Dr; No, did not have]
2. Has a doctor ever actually said that your child has eczema? (10 & 14 years only) [yes; no]

We defined cases as those individuals who answered 'Yes, and saw a Dr' to Q1 or 'yes' to Q2. We defined controls as those individuals who answered 'no' to Q2 at age 14 years.

Discovery Cohort Genotyping and Statistical Analysis

Subjects were genotyped using either Illumina 317K or 610K genome-wide SNP genotyping platforms by the Wellcome Trust Sanger Institute, Cambridge, UK and the Centre National de Génotypage, Evry, France. A common set of SNPs were extracted and the resulting raw genome-wide data was subjected to standard quality control methods. Individuals were excluded on the basis of having incorrect gender assignments; minimal (0.34) or excessive (0.36) heterozygosity; disproportionate levels of individual missingness (>3%) and evidence of cryptic relatedness (PI HAT > 0.11). The remaining individuals were assessed for evidence of population stratification by multidimensional scaling analysis, using CEU, Yoruba, Japanese and Chinese individuals as reference ethnic groups. The underlying population stratification was thereafter controlled for by using EIGENSTRAT derived ancestry informative covariates. SNPs with a minor allele frequency of < 0.5% and call rate of < 97% were removed. Furthermore, only SNPs which passed an exact test of Hardy-Weinberg equilibrium (P > 5E-7) were considered for analysis. The resulting dataset consisted of 3233 individuals and 285,531 SNPs. Missing genotypes were subsequently imputed with MACH 1.0 Markov Chain Haplotyping software, using CEPH individuals from phase two of the HapMap project as a reference set (release 22). The final imputed dataset consisted of 3233 subjects, each with 2,483,534 imputed markers. 2811 of which also had AD phenotype information (909 cases and 1902 controls).

Genome-wide association analysis of AD was carried out in MACH2DAT [3,4] regressing expected allelic dosage on case-control status, including sex as a covariate.
R501X and 2282del4 have been genotyped in a previous study on 2634 subjects[5]. In the FLG adjusted analysis, these were included as covariates (using an additive model).

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 > 5E-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, 2903 also had AD phenotype information (895 cases and 2008 controls) and were not included in the ALSPAC discovery set.

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

BAMSE

BAMSE is a Swedish birth cohort study. A total number of 4,089 newborn infants were recruited between 1994 and 1996 in the Stockholm area[6]. The first questionnaire data, dealing with parental allergic diseases, socio-economic status and residential characteristics, was obtained when the children were about 2 months. Similar questionnaires with a focus on the children's symptoms related to asthma and allergic diseases including eczema were answered by the parents when the children were approximately 1, 2, 4 and 8 years old. At 8 years of age, all children were invited to clinical testing, and blood samples were obtained from 2,480 children (~60%). DNA was extracted from 2,033 samples after exclusion of samples with too little blood, lack of questionnaire data, or if parental consent to genetic analysis of the sample was not obtained. From these samples, all children with a doctor's diagnosis of asthma (ever) and children with no history of eczema or other allergic diseases (controls) underwent GWAS genotyping[7]. Among asthmatics, all children with doctor's diagnosis of eczema (ever) were identified and after QC, a total of 100 eczema (ever) cases and 246 controls were included in this study.

BAMSE genotyping was conducted as part of the GABRIEL consortium. Genotyping in GABRIEL was carried out at Centre National de Génotypage (Evry, France) using the Illumina Human610 quad array (Illumina, Inc., San Diego, CA)[7]. An ancestry analysis was performed using EIGENSTRAT, and putative non-Caucasian samples were flagged as outliers and eliminated from subsequent analyses. Imputation to HapMap CEU release 22 was conducted using MACH v.1.0.16 with option MLE (original genotypes were only replaced if the underlying reference haplotypes strongly contradict the input genotypes). Samples from the British 1958 birth cohort (B58C) with greater than 95% genotyping success rate were selected to estimate model parameters of error rates and recombination rates for step 1 of the imputation procedure. In step 2, all GABRIEL cohorts were imputed, no SNP/sample QC filters were applied to individual cohorts prior to this.

Genome-wide association analysis of AD was carried out in ProbAbel[8] regressing expected allelic dosage on case-control status, including sex as a covariate. The study was approved by the Ethics Committee of Karolinska Institutet, Stockholm, Sweden.

British 1958 birth cohort (B58C)

The British 1958 birth cohort is an ongoing follow-up of all persons born in England, Scotland and Wales during one week in 1958. At age 7 years, a history of eczematous rashes was obtained by interview with a parent, and the presence of visible AD on skin examination was recorded by a school medical officer[9]. For the purpose of this meta-analysis, cases were defined by a positive interview response for either AD during the first year of life, or AD after the first year (ie. ages 1-7), or both. (The results of skin examination were not used to define cases.) Controls were defined as children with no parentally reported history of AD by age 7, and no record of AD on skin examination at age 7.

At the age of 44-45 years, the cohort were followed up with a biomedical examination and blood sampling [10], from which a DNA collection was established as a nationally representative reference panel (http://www.b58cgene.sgul.ac.uk/). 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) [11] and the Type 1 Diabetes Genetics Consortium (T1DGC)[12]. 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 [7] and by the WTCCC on cohort members that had not been included in the discovery sets. Imputations for the replication set using the HapMap 2 (release 21) template were performed using MACH and within-cohort logistic regression analyses for eczema were performed using ProbAbel.

CHOP

CHOP patients and controls were recruited at the Children's Hospital of Philadelphia between 2006 and 2010. All subjects were of self-reported Caucasian origin and resident in the Greater Philadelphia area. Ethical approval for this study was obtained from the Institutional Revue Board of the Children's Hospital of Philadelphia. The study included 519 patients with physician-diagnosed eczema and 1004 disease-free controls without eczema. Cases were defined by the presence of the ICD9 code for eczema (691.8) in their electronic medical records. 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[13-15]. 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. The families used doctors employed at the clinical research unit, and not the family practitioner, for diagnosis and treatment of AD and other skin-related symptoms. Skin lesions were described at both scheduled visits at 6-monthly intervals and acute visits with skin symptoms according to pre-defined morphology and localization; AD was defined based on the Hanifin-Rajka criteria as previously detailed[16-18].

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[19].

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

Danish National Birth Cohort (DNBC)

DNBC is a population-based cohort of more than 100,000 pregnancies, recruited in the years 1996-2002[20]. Extensive phenotype information was collected by computer-assisted telephone interviews twice during pregnancy as well as 6 and 18 months after delivery. An additional questionnaire-based follow-up survey was conducted when the children reached 7 years of age. Cases with early onset AD were identified from the 18 months telephone interview data using an algorithm specifically developed for this purpose[21]. In addition, children with a positive response to both of the following two questions from the 7 year survey were included in the case group: 1) "Has a doctor ever said that your child had AD, also known as allergic rash?" and 2) "Has your child ever had an itchy rash which was coming and going for at least 6 months?". Finally, children with ICD10 diagnosis code L20 in the Danish Hospital Discharge Register were also included in the case group. Controls were required not to have any AD or AD symptoms recorded in interview, questionnaire, or register data. GWAS data were generated for 3,840 individuals from the DNBC (mothers and their children) in a study of prematurity and its complications (Principal investigator Jeff Murray) within the Gene Environment Association Studies (GENEVA) consortium. AD information and genome-wide genotype and imputed data were available for 1,641 children. Imputation was carried out with MACH, using HapMap CEU release 22 as the reference panel. Logistic regression analysis for AD was performed with MACH2DAT, using imputed allele dosages and including sex as a covariate.

The DNBC study protocol was approved by the Danish Scientific Ethical Committee and the Danish Data Protection Agency.

ECRHS

Details of the methods of ECRHS I and ECRHS II, a multicentre international cohort study, have been published elsewhere[22,23]. Participants within the ECRHS were eligible for inclusion in this analysis if they were identified by random sampling of those who fulfilled the following criteria 1) lived in centres that took part in genome-wide genotyping initiative under the auspices of GABRIEL[7] AND 2) were initially selected to take part in the ECRHS clinical measurements as part of the random sample (ie not specifically selected for inclusion because of any pre-existing disease). Cases were those answering positively to the questions 'Have you ever had an itchy rash that was coming and going for at least 6 months?' AND yes to 'Have you had this itchy rash in the last 12 months?' during ECRHS II (aged 27-58). Further information on the distribution of eczema within the cohort is available[24].

Genotyping and imputation was carried out within the GABRIEL consortium, details in BAMSE methods (page S5). Genome-wide association analysis of AD was carried out in ProbABEL regressing expected allelic dosage on case-control status, adjusted for sex, recruitment centre and first two principal components informative of European ancestry.

Each participating centre obtained ethical permission from the appropriate local committee.

Generation R

The Generation R Study is a population-based prospective cohort study of pregnant women and their children from fetal life onwards in Rotterdam, The Netherlands[25,26]. All children were born between April 2002 and January 2006, and currently followed until young adulthood. Of all eligible children in the study area, 61% were participating in the study at birth[26]. Cord blood samples including DNA have been collected at birth. Postnatal data about eczema was annually collected by questionnaires at the ages of 1 to 5 years. Response rates for the questionnaires were 71%, 76%, 72%, 73% and 74%, respectively[26]. For the current study, 1,115 children were included in the discovery analysis (males, n = 594 (53%)). A total number of 620 children were available for the replication analyses (males, n = 299 (48%). Questions about eczema were 'Has your child in the past 12 months had eczema [yes, saw a doctor; Yes, but did not see a doctor; No, did not have] (age 1 to 4 years)?' and 'Has your child ever had eczema [yes; no] (age 5)?'. We defined cases as those children of whom parents answered their child 'Yes, had eczema and saw a doctor' or 'Yes, ever had eczema'. We defined controls as those children of whom parents answered their child 'No, never had eczema' and 'Yes, had eczema but did not see a doctor/No, did not have eczema'. The current study used the first set of Generation R samples of Northern European Ancestry. Samples were genotyped using Illumina Infinium II HumanHap610 Quad Arrays following standard manufacturer's protocols. Intensity files were analyzed using the Beadstudio Genotyping Module software v.3.2.32 and genotype calling based on default cluster files. Any sample displaying call rates below 97.5%, excess of autosomal heterozygosity (F<mean-4SD) and mismatch between called and phenotypic

gender were excluded. In addition, individuals identified as genetic outliers by the IBS clustering analysis (> 3 standard deviations away from the HapMap CEU population mean) an one of 2 pairs of identical twins (IBD probabilities =1) were excluded from the analysis. After quality control (QC) 2,729 children were included in the analyses. Genotypes were imputed for all polymorphic SNPs from phased haplotypes in autosomal chromosomes of the HapMap CEU Phase II panel (release 22, build 36) oriented to the positive (forward) strand. Genotyped SNPs with minor allele frequency < 0.01, SNP Call Rate < 0.98 and HWE P-value < $1x10^{-6}$ were filtered. After marker pruning 503,248 SNPs were used for imputation (MACH v 1.0.16) of 2,543,887 SNPs. Association analysis for directly genotyped data were carried out in PLINK implemented on BCSNPmax and for imputed data were ran using MACH2DAT implemented in the GRIMP[27] user interface platform. The study protocol was approved by the Medical Ethical Committee of the Erasmus Medical Centre, Rotterdam (MEC 217.595/2002/20). Written informed consent was obtained from all participants.

Genetics of Overweight Young Adults (GOYA) women's study

In total, 91,387 pregnant women were recruited to the Danish National Birth Cohort during 1996-2002, 67,853 of whom gave birth to a live born infant and had provided a blood sample during pregnancy. The GOYA study includes a subset of these women, selected for genome-wide genotyping according to their BMI and is described in full elsewhere[28,29]. The 4% (2,451) of the women with the largest residuals from the regression of BMI on age and parity and a random sample of similar size (2,450) drawn from the remaining distribution were selected for genotyping. Pertinent to this study, the women were asked questions about eczema during a telephone interview at ~16 weeks of gestation. The questions were:

1. Have you ever had any skin disease?
2. Was the skin disease diagnosed by a doctor?
3. What kind of skin disease?

Cases were defined as those that answered "yes" to Qs 1 and 2, and 'AD' to Q3. Controls were defined as those that answered "no" to Q1.

The GOYA study was approved by the regional scientific ethics committee and by the Danish Data Protection Board.

Genome-wide genotyping on the Illumina 610k quad chip was carried out at the Centre National de Génotypage (CNG), Evry, France. We excluded SNPs with minor allele frequency <1%, >5% missing genotypes or which failed an exact test of Hardy-Weinberg equilibrium (HWE) in the controls (p<10-7). We also excluded any individual who did not cluster with the CEU individuals (Utah residents with ancestry from northern and western Europe) in a multidimensional scaling analysis seeded with individuals from the International HapMap release 22, who had >5% missing data, outlying heterozygosity of >35% or <30.2%, both samples in the case of genetic duplicates, one of each pair of genetically related individuals, individuals with sex discrepancies and individuals whose genotyping was discordant with a previous project. After data cleaning, 3,908 women and 545,349 SNPs remained. We carried out imputation to HapMap release 22 (CEU individuals) using Mach 1.0, Markov Chain Haplotyping[3,4].

Logistic genome-wide association analysis for AD (with no covariates) was carried out in MACH2DAT[3,4].

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 the question about atopic dermatitis. The participation rate was higher among older age-groups than among younger age groups in both genders[30]. 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 participants were mailed a standard invitation letter and a questionnaire about health, lifestyle, and socioeconomic factors. AD was defined by the U.K. Working Party's diagnostic criteria for atopic dermatitis as a history of an itchy skin condition plus a minimum of two of four minor criteria[31].

Genotyping of SNPs was performed by the PCR KASPar genotyping system (KBiosciences, Hoddesdon, UK). None of the SNPs deviated from HW equilibrium ($p>0.05$ for all SNPs). 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

The Cooperative Health Research in the Region of Augsburg (KORA) study is a series of independent population-based epidemiological surveys and follow-up studies of participants living in the region of Augsburg, Southern Germany[32]. All participants are of German nationality identified through the registration office and informed consent has been given by all participants. The study has been approved by the local ethics committee. Participants were examined in 1994/95 (KORA S3) or 1999/2001 (KORA S4) and in the follow-up examinations in 2004/05 (KORA F3) and 2006/08 (KORA F4). All KORA subjects had completed a standardized questionnaire which next to demographic data included the basis allergy questions of the European Community Respiratory Health Survey (ECRHS) on respiratory health[22]. AD was diagnosed based on a reported physician's diagnosis in the past. For the genome-wide association study we genotyped 1,644 randomly selected participants of KORA F3 using Affymetrix 500K and 1,814 randomly selected participants of KORA F4 using Affymetrix 6.0[33]. Genome-wide association analysis of AD was carried out using logistic regression in SNPTEST V2 (http://www.stats.ox.ac.uk/~marchini/software/gwas/snptest.html), including sex as a covariate.

For replication purpose 1100 AD cases of self-reported German ethnicity were obtained from the GENEVA (Genetic evaluation of atopic dermatitis) study from the Department of Dermatology and Allergy, Technical

University Munich[34]. AD was diagnosed on the basis of a skin examination by experienced dermatologists according to standard criteria in the presence of a chronic or chronically relapsing pruritic dermatitis with the typical morphology and distribution[35]. KORA controls were selected of the remaining KORA F4 sample which was not included in the GWAS analysis. De novo replication analysis was carried with R 2.12.2 (http://www.R-project.org) using logistic regression adjusted for sex. Genetic information entered the model as allele counts.

LISA/GINI

The influence of Life-style factors on the development of the Immune System and Allergies in East and West Germany PLUS the influence of traffic emissions and genetics (LISAplus) Study is a population based birth cohort study. A total of 3097 healthy, fullterm neonates were recruited between 1997 and 1999 in Munich, Leipzig, Wesel and Bad Honnef. The participants were not pre-selected based on family history of allergic diseases[36].

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[37]. All children without a family history of allergic diseases and children whose parents did not give consent for the intervention were allocated to the non-interventional arm. Detailed descriptions of the LISAplus and GINIplus studies have been published elsewhere [36] and [37], respectively).

Information on ever having physician-diagnosed AD was collected using self-administered questionnaires completed by the parents. The questionnaires were completed at 6, 12, 18 and 24 months and 4, 5, 6 years of age in the LISAplus study and 1, 2, 3, 4 and 6 years in the GINIplus study asking for each year of age since the previous follow-up. DNA was collected at the age 6 and 10 years. For both studies, approval by the local Ethics Committees and written consent from participant's families were obtained.

In the discovery analysis, 379 children from the LISAplus study from Munich were included (number of boys: 227 (57%)). 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[38].

Genome-wide association analysis of AD was carried out in SNPTEST V1 (http://www.stats.ox.ac.uk/~marchini/software/gwas/snptest.html) regressing expected allelic dosage on case-control status, including sex as a covariate.

For replication, 665 children from Munich from both studies were included (499 (75%) children from the GINIplus study and 166 (25%) children from the LISAplus study)). 583 individuals (499 from the GINIplus study and 84 from the LISA study) were analysed using the Affymetrix Human SNP Array 5.0 and 82 individuals from the LISAplus study were analysed using Affymetrix Human SNP Array 6.0. Genotypes were called using BRLMM-P algorithm (5.0), respectively BIRDSEED V2 algorithm (6.0), imputed in IMPUTE2[39] and genome-wide

association analysis of AD was carried out in SNPTEST V2 (http://www.stats.ox.ac.uk/~marchini/software/gwas/snptest.html) regressing expected allelic dosage on case-control status, including sex as a covariate.

Manchester Asthma and Allergy Study (MAAS)

The Manchester Asthma and Allergy Study is an unselected, population-based prospective study which follows the development of atopic disorders in a cohort of children described in detail elsewhere[40-44]. 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. Informed consent was obtained from all parents.

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 and 8 years (±4 weeks).

Definitions of outcomes

AD: Information on the age of onset of parentally-reported AD was collected using an interviewer-administered validated ISAAC questionnaire to collect information on parentally reported symptoms, physician-diagnosed illnesses and treatments received.

In this analysis eczema was defined as a positive answer to the question "Has your child ever suffered from eczema?". The association study was carried out in the 761 MAAS individuals for which both genotype and phenotype data was available.

Genotyping

DNA samples were genotyping on an illumina 610 quad chip. The illumina genotypes were called using the Illumina GenCall application following the manufacturer's instructions. Quality control criteria for samples

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

The Norwegian Mother and Child Cohort Study (MoBa)

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health[45,46]. Participants were recruited from all over Norway from 1999-2008, and 38.5% of invited women consented to participate. The cohort now includes 108,000 children, 90,700 mothers and 71,500 fathers. Blood samples were obtained from both parents during pregnancy and from mothers and children (umbilical cord) at birth. Follow-up is conducted by questionnaires at regular intervals and by linkage to national health registries.

The current study is based on version 4 of the quality-assured data files and included participants that were recruited between 1999-2005. Informed consent was obtained from each MoBa participant upon recruitment. The study was approved by The Regional Committee for Medical Research Ethics in South-Eastern Norway and the Norwegian Data Inspectorate.

The cases were indentified from questionnaires at the child's age 6, 18 and 36 months defined by the following questions: Does your child have or has he/she had any of the following health problems? Atopic eczema was listed as one of several items here. If yes was entered on the first question, a second were asked: has the mother and child health care centre or someone else referred your child for further specialist investigation Our cases were restricted to unique cases across age 6, 18 and 36 months with yes on both questions. Consequently the controls were unique controls across age 6, 18 and 36 months with no on both questions.

The genotype platform used were Illumina 660W and imputed SNPs were only included if the met the recommended threshold for imputation quality (PLINK INFO >0.8). Logistic regression analyses for AD was performed using an additive model in PLINK, including sex as a covariate. The children included in this study are originally genotyped for a case control study (n=1200 children) of spontaneous preterm delivery.

The Northern Finland Birth Cohort 1966 (NFBC66)

The Northern Finland Birth Cohort 1966 is a prospective follow-up study of children from the two northernmost provinces of Finland[47]. Women with expected delivery dates in 1966 were recruited through maternity health centres[48]. Cohort members living in northern Finland or in the capital area were invited to a clinical examination as well as questionnaire at age 31 years. DNA was extracted from blood samples given at the clinical examination[49]. For the purpose of this meta-analysis, we included data from the following questions:

1. Have you had eczema (infantile, atopic or allergic)?
2. If yes, have you ever been treated by a doctor

Individuals who answered yes to both questions were defined as cases (1208). Individuals that answered no to the first question were defined as controls (2294). Genotyping was completed at the Broad Institute Biological Sample Repository in participants with available DNA using Illumina HumanCNV370DUO Analysis BeadChip array for 339,629 SNPs. We excluded 3,345 SNPs from analysis because HWE was not met at a level p <0.0001, 55 because of low call rate (<95%) and 7,681 because the MAF was <1%, leaving 329,091 SNPs for the association analysis. Imputation was conducted using the algorithm implemented in IMPUTE and association analysis using quicktest[50]. Informed consent for the use of the data including DNA was obtained from all subjects. The study was approved by the ethics committees in Oulu (Finland) and Oxford (UK) universities in accordance with the Declaration of Helsinki.

Northern Finland Birth Cohort 1986 (NFBC86)

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)[51]. At the age of 16, the cohort members were sent a postal questionnaire including questions on eczema, 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. For the purpose of this meta-analysis, we included data from 1717 individuals that answered the following questions:

1. Have you ever had eczema which has been called infantile eczema, atopic eczema or allergic eczema?
2. Diagnosed or treated by a doctor?

Individuals who answered yes to both questions were defined as cases (316). Individuals that answered no to the first question were defined as controls (1401). Genotyping was performed by KBiosciences (Hoddesdon) using their own system of fluorescence-based competitive allele-specific PCR (KASPar) with genotype success rate >97%. Association analysis was conducted using quicktest[50]. 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.

Netherlands Twin Register (NTR)

The Netherlands Twin Register (NTR) is a large population based study that registers approximately 40% of all multiple births in the Netherlands since 1986[52]. At age 5 of the children, a survey is sent out in which the

parents of the twins are asked to indicate for each child separately whether a doctor has ever diagnosed eczema. A similar question concerns doctor diagnosed baby eczema[53].

Blood and/or buccal samples for DNA extraction were collected for a subsample of the NTR in several projects. Genotyping was performed on the Affymetrix Human SNP Array 6.0 in the Avera Institute, Sioux Falls, South Dakota (USA). Genotypes were called using the BIRDSEED V2 algorithm and imputed in BEAGLE in the MD Anderson Cancer Center, Houston, Texas (USA). After QC, one individual of each family was selected. If both twins were cases or controls, one individual was picked at random, otherwise the case was selected. A total of 123 cases and 306 controls were included in the study. Logistic regression analyses were performed using an additive model in PLINK, including sex as a covariate. The study was approved by the Medical Ethical Committee of the VU Medical Centre, Amsterdam, the Netherlands (IRB00002991).

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[54]. 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[7]. For this, 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, 186 cases of eczema and 167 controls were selected for the current study. Cases of eczema were defined as parental reported doctor diagnosed eczema ever at age 2 years or doctor diagnosed eczema in the last 12 months at ages 3, 4, 5, 6 ,7 or 8 years. Controls were defined as children whose parents denied the presence of doctor diagnosed eczema in the last 12 months at all ages. Genotyping was performed with an Illumina Human610 quad array. SNPs were excluded that fullfilled one or more of the following criteria: p-value for test of Hardy-Weinberg equilibrium $\leq$ 1E -7, genotyping call rate <95% or MAF < 1%. SNPs were imputed with IMPUTE version 2 software using HAPMAP CEU release #22 b36. Genome-wide association analyses were performed using SNPTEST version 1.1.5. The Medical Ethical Committees of the participating institutes approved the study.

QIMR discovery cohort

We recently performed a GWAS of asthma in 2,832 unrelated individuals of European ancestry ascertained from the Australian population as described in detail elsewhere[55]. Of these, 2,148 individuals (34% males, mean age 32 years, range 10 to 92) reported information on their AD status in health questionnaires, including

482 individuals who reported having had AD at any point in their lifetime (32% diagnosed by a doctor) and 1,666 AD-free controls. Genotyping was performed with Illumina 610K or 370K arrays and stringent quality control filters applied as described in Supplementary Table 2. Imputation of HapMap 2 SNPs (CEU release 21) was performed with MACH and SNPs tested for association with disease status using logistic regression in PLINK, with sex included as a covariate. Participants provided informed consent to participate in this study, which was approved by the QIMR ethics committee.

Western Australian Pregnancy (Raine) cohort

Recruitment of the Western Australian Pregnancy (Raine) cohort has previously been described in detail[56-58]. 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 21 years of age (average ages of one, two, three, six, eight, ten, 14, 17 and currently 21) 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, 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[56]. 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.

SAPALDIA

SAPALDIA data are derived from among 6,055 SAPALDIA cohort subjects that participated in both, the baseline (1991) and follow-up (2002) examinations and agreed to providing blood for genetic analysis.

SAPALDIA is a population-based cohort that originally recruited subjects aged 18 to 60 from population registries in eight Swiss communities representing the three largest language groups (German, French, Italian) as well as different levels of air pollution, altitude and degrees of urbanization[59,60]. At both baseline and follow-up examination subjects underwent spirometry as well as a detailed interview on respiratory health and allergies, smoking history, lifestyle factors and anthropometry. At follow-up, 8,047 of 9,651 baseline subjects re-participated in at least one part of the study and a formal biobank was established. AD was defined as positive answer to the question "Have you ever had atopic dermatitis or any other kind of skin allergy?" at either examination. The basis for this study formed control subjects and a random sample of all asthmatics (sampled proportionally to the overall asthma prevalence in the study) that were part of a nested asthma case-

control sample subjected for genomewide genotyping in the context of the GABRIEL genome-wide association study on asthma[7]. Genotyping and imputation was carried out within the GABRIEL consortium, details in BAMSE methods (page S5).

Association analysis was performed in ProbABEL. All study participants gave written informed consent, and the study was approved by the national and respective cantonal ethics committees.

The Department of Twin Research and Genetic Epidemiology at King's College London (TwinsUK)

The TwinsUK adult twin registry based at St Thomas' Hospital in London is a volunteer cohort of over 12,000 identical and non-identical twins[61] recruited since 1993. The cohort is predominantly female (92%). Twins largely volunteered unaware of the study in which they would subsequently be included, gave fully informed consent under a protocol reviewed by the St Thomas' Hospital Local Research Ethics Committee.

Subjects were genotyped using Illumina's Human Hap 300k Duo and Human Hap610 Quad. Genotyping was performed in part at the Wellcome Trust Sanger Institute (Hinxton, UK) and in part at the Center for Inherited Disease Research, NIH, Baltimore, MD, United States. Genotypes were quality controlled and were excluded from the analysis for low genotype rate defined as less than 95% for alleles with a minor allele frequency (MAF) of 0.05 and above or less than 99% for loci with a MAF of 0.05 or below or for Hardy-Weinberg disequilibrium ($p<0.0001$). Individual samples were included in the analysis if they were of non-admixed Caucasian descent, did not show lack or excess heterozygocity, had high (defined as in excess of 99% success rate) individual genotypes available.

Genotypes were imputed using IMPUTE 2.0 using Linkage Disequilibrium patterns observed in the HapMap 2 CEU population as a template. A total of 1,236 unrelated subjects for which both genetic and phenotypic information was available was analyzed using PLINK.

Collaborating Consortia Members

AAGC - Australian Asthma Genetics Consortium

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LISA/GINI

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Supplementary Table 1. Study characteristics - discovery & replication

Cohort	Type	N	Percent male	Mean age @ interview	Atopic dermatitis question	Physician diagnosis required	Case response	case #	Control response	control #
Discovery cohorts										
ALSPAC	Birth cohort	2811	50%	81m, 91m, 103m, 10y, 13y, 14y	1. Has your child in the past 12 months had eczema?		1. Yes, and saw a Dr			
				10y, 14y	2. Has a doctor ever actually said that your child has eczema?		2. Yes		2. No (@ 14 y)	
						yes	Yes to 1 or 2 at any timepoint	909		1902
B58C-WTCCC	Birth cohort	1285	50%	7y	1. Parent interview: History of atopic dermatitis in first year?		1. Yes			
				7y	2. Parent interview: History of atopic dermatitis after first year?		2. Yes			
				7y	3. Medical examination					
						no	Yes to 1 or 2	103	No to 1 and 2 and 3	1182
B58C-T1DGC	Birth cohort	2186	48%	7y	1. Parent interview: History of atopic dermatitis in first year?		1. Yes			
				7y	2. Parent interview: History of atopic dermatitis after first year?		2. Yes			
				7y	3. Medical examination					
						no	Yes to 1 or 2	188	No to 1 and 2 and 3	1998
CHOP	Population based cohort	1523	51%	9y	ICD9 diagnosis in electronic medical record	yes		519		1004
COPSAC	Birth cohort	332	49%	0-6y	Diagnosis prospectively by dermatologist at the research unit based on Hanifin-Rajka criteria	yes	Diagnosed atopic dermatitis	171	No atopic dermatitis diagnosis and followed up to 6 yr	161
DNBC	Birth cohort	1641	52%	18m	1. Has your child had itchy rash?		1. Yes			
				18m	2. Has a doctor told you that your child had atopic dermatitis?		2. Yes			
				18m	3. Was the rash recurrent?		3. Yes			
				18m	4. In which 0.5 month periods did your child have the rash?		4. Rash for at least 4 consecutive 0.5-month periods			

				18m	5. Where was the rash located?		5. Localization in elbow creases, behind the knees, face, wrists/hands or generalized/4 or more localizations			
				7y	6. Has your child ever had atopic dermatitis?		6. Yes			
				7y	7. Has your child ever had an itchy rash which was coming and going for at least 6 months?		7. Yes			
					9. Hospital Discharge Record of ICD10 code L20					
						no	[Yes to 1 or 2 and Yes to 3 or 4 and 5] or [Yes to 6 and 7] or 9	225	No AD or AD symptoms recorded in interview, questionnaire, or register data	1416
Generation R	Birth cohort	1115	53%	1y, 2y, 3y, 4y	1. Has your child had atopic dermatitis in the last 12 months for which he/she attended a general practitioner/hospital?					
				5y	2. Has your child ever had atopic dermatitis?					
						no	Yes to 1 (at any timepoint) or 2	676	No to 1 and 2	439
GOYA	Mothers from birth cohort	3359	0%	29y	1. Have you ever had any skin disease?	yes	Yes to 1 and 2 and 'atopic dermatitis' to 3	180	No to 1	3179
					2. Was the skin disease diagnosed by a doctor?					
					3. What kind of skin disease?					
KORA F3	Cohort study	1375	49%	61y	1. Did a physician ever diagnose you with atopic eczema?	yes	Yes	42	No	1333
KORA F4	Cohort study	1791	49%	61y	1. Did you ever have atopic dermatitis/eczema?					
					2. If yes, was it diagnosed by a physician?					
						yes	Yes to 1 and 2	101	No to 1 or 2	1690
LISA	Birth cohort	379	57%	6m, 12m, 18m, 24m	1. Did a physician diagnose your child having atopic dermatitis in the past 6 months?		1. Yes			
				4y, 5y, 6y	2. Did a physician diagnose your child having atopic dermatitis in the past 12 months?		2. Yes			
						yes	Yes to 1 or 2 at any timepoint	93	No to all of the time points	286
NFBC66	Birth cohort	3502	47%	31y	1. Have you had eczema (infantile, atopic or allergic)?		1. Yes			
					2. if yes, have you ever been treated by a doctor		2. Yes			
						yes	Yes to 1 and 2	1208	No to 1	2294

PIAMA	Birth cohort	353	53%	3m,1y,2y,3y,4y,5y,6y, 7y,8y	1. Has your child ever had atopic dermatitis?		1. Yes			
				2y,3y,4y,6y,7y,8y	2. Did a doctor ever diagnose atopic dermatitis in your child?		2. Yes			
				2y,3y,4y,6y,7y,8y	3. Did your child have atopic dermatitis during the past 12 months?		3. Yes			
						yes	Yes to 1 and 2 and 3	186	No to 1 and 2 and 3 at ages 2-8	167
RAINE	Birth cohort	1135	53%	5y	1. Do you think your child has ever had atopic dermatitis? Has anyone ever told you your child has atopic dermatitis?[yes and who(paediatrician, GP, child health nurse, naturopath, friend, relative)		1. Yes			
				8y	2. Has your child had atopic dermatitis in the last 12 month?					
						yes	Yes to 1 and were diagnosed by a paediatrician/GP	245	No to 1 and 2 (subject excluded in case of missing).subjects who answered 'Yes' to 1 and were diagnosed to someone other than a paediatrician/GP were coded as missing	890
QIMR	Population based cohort	2148 (adolescent=765, asthma=55, adult=1328)	34%	Mean=32, SD=15, range=10-92	1. Adolescent/Asthma study: Have you (your child) ever had eczema confirmed by a doctor?		1. Yes		1. No	
					2. Adult study: How often have you had any eczema? [“Only as a child”, “Quite often”, “Sometimes”, “Often”, "Never"]		2. Yes to “Only as a child”, “Quite often”, “Sometimes” or “Often”		2. Yes to “Never“	
						no	Yes to 1 or 2	482	No to 1 or 2	1666
Twins UK	cohort study	1236	8%	46 years	1. Have you ever had eczema?	no	Yes	278	No	958

Replication cohorts										
AAGC		3881	49%	Mean=35, SD=17, range=3-89						
	Population base cohort	QIMR			1. QIMR study: Have you (your child) ever had eczema confirmed by a doctor?	yes	1. Yes	241	1. No	2891
	Birth cohort	CAPS			2. CAPS study: Has your child ever had eczema confirmed by a doctor?	yes	2. Yes	28	2. No	25
	Population based cohort	LIWA						0		474
	Birth cohort	MESCA						0		64
	Birth cohort	TAHS						0		158
						yes	Yes to 1 or 2 at any timepoint	269		3612
ALSPAC	Birth cohort	2903	50%	81m, 91m, 103m, 10y, 13y, 14y	1. Has your child in the past 12 months had eczema?		1. Yes, and saw a Dr			
				10y, 14y	2. Has a doctor ever actually said that your child has eczema?		2. Yes		2. No (@ 14 y)	
						yes	Yes to 1 or 2 at any timepoint	895		2008
BAMSE	Birth cohort	346	Cases: 62%	1y, 2y, 4y, 8y	1. Has a doctor diagnosed your child as having atopic dermatitis after the age of x year		1. Yes			
			Controls:48%	1y	2. Has a doctor ever diagnosed your child as having atopic dermatitis up to 1 year of age		2. Yes			
						yes	Yes to 1 and/or 2	100	No to both Q at all times	246
B58C-REPL	Birth cohort	2090	51.3%	7y	1. Parent interview: History of atopic dermatitis in first year?		1. Yes			
				7y	2. Parent interview: History of atopic dermatitis after first year?		2. Yes			
				7y	3. Medical examination					

						no	Yes to 1 or 2	170	No to 1 and 2 and 3	1920
ECRHS	Population based cohort study. Information provided is based on follow-up	1650	49.03%	42.8 (7.1)	1. Have you ever had an itchy rash that was coming and going for more than six months?		1. Yes			
					2. Have you had this itchy rash in the last 12 months?		2. Yes			
						no	Yes to 1 and 2	176	No to 1 or 2	1474
Generation R	Birth cohort	620	48%	1y, 2y, 3y, 4y	1. Has your child had eczema in the last 12 months for which he/she attended a general practitioner/hospital?					
				5y	2. Has your child ever had eczema?					
						no	Yes to 1 (at any timepoint) or 2	182	No to 1 and 2	438
Health2006	Population based cohort	3329	44.7%	49.4 years	The U.K. Working Party's diagnostic criteria for atopic dermatitis as a history of an itchy skin condition plus a minimum of two of four minor criteria were used. The major criteria was an itchy skin condition and the minor criteria were: 1) a history of involvement of the skin creases, 2) a personal history of asthma or hay fever, 3) a history of general dry skin in the last year, 4) onset under the age of 2 years.	no	AD cases according to U.K. Working Party's diagnostic criteria for atopic dermatitis	337	non-AD U.K. Working Party's diagnostic criteria for atopic dermatitis	2992
KORA F4	Population based controls	1100	49%	25.4	1. Did a physician ever diagnose you with atopic dermatitis/eczema?					
					2. Dermatologic examination, UK Working Party Criteria					
GENEVA	Tertiary care cases	1100	42%	49.3	1. Did a physician ever diagnose you with atopic dermatitis/eczema?					

					2. Dermatologic examination, UK Working Party Criteria		Yes to 1 and actual dermatologist's diagnosis	1100	No to 1 and no actual dermatologist's diagnosis	1100
						yes	Yes to 1	1100	No to 2	1100
LISA/GINI	Birth cohort	665 (GINI: 499, LISA: 166)	51%	LISA: 6m, 12m, 18m, 24m	1. Did a physician diagnose your child having atopic dermatitis in the past 6 months?		1. Yes			
				LISA: 3y-6y, GINI: 1y-6y	2. Did a physician diagnose your child having atopic dermatitis in the past 12 months?		2. Yes			
						yes	Yes to 1 or 2 at any timepoint	231	No to all of the time points	434
MAAS	Unselected birth cohort	761	55%	1y, 3y, 5y, 8y	1. Has your child ever suffered from atopic dermatitis	no	'Yes' at any timepoint	435	No	326
MoBa	Pregnancy cohort	937	51%	6m, 18m, 36m	1. Does your child have or has he/she had any of the following health problems? (Enter a cross in a box for each item.) Atopic eczema (childhood eczema) - listed as an item		1. yes			
					2. If yes, has the mother and child health centre or someone else referred your child for further specialist investigation?		2. yes			
						yes	Yes to 1 and 2 at any timepoint	70	No to all of the time points	867
NFBC86	Birth cohort	4465	50%	15-16y	1. Have you ever had eczema which has been called infantile eczema, atopic eczema or allergic eczema?					
					2. Diagnosed or treated by a doctor?	yes	yes to 1+2	798	no to 1	3667
NTR	Population based cohort study	429	50.8%	5y	1. Did a physician since birth ever diagnosed your children with eczema? (Oldest/youngest answered seperately)					
					2. Did a physician since birth ever diagnosed your children with baby eczema? (Oldest/youngest answered seperately)					
						yes	Yes to 1 or 2	123	1. No to 1 and 2	306

SAPALDIA	Population based cohort study.	976	50%	2 examinations: baseline in 1991, follow-up in 2002. Age (sd) in 2002: 53.2 (11.1)	Have you ever had atopic dermatitis or any other kind of skin allergy?	no	Yes. At either of the 2 examinations (1991 & 2002)	533	No' at both examinations 'No' at follow-up, if missing at baseline ('No' at baseline & missing at follow-up set to missing)	443

Supplementary Table 2. Study genetic & analysis methods (a) discovery and (b) replication cohorts

(a)

	Genotyping		BEFORE IMPUTATION QUALITY CONTROL PER SUBJECT				BEFORE IMPUTATION QUALITY CONTROL PER SNP				IMPUTATION			DATA ANALYSIS	
Cohort	**Genotyping Platform**	**Genotype-Calling Algorithm**	**call rate threshold**	**heterozygosity thresholds**	**ethnicity exclusions**	**other exclusion criteria**	**SNP call rate**	**HWE p-value threshold**	**MAF threshold**	**other exclusion criteria**	**Imputation Software (Version)**	**HapMap CEU Release**	**NCBI Build**	**Association Software**	**GWAS Lambda**
ALSPAC	Illumina 317K or 610k		0.97	0.34 & 0.36	MDS - eigenstrat adjusted	sex discrpeancies, related individuals	0.97	5E-07	0.005	no	MACH 1.0	22	36	MACH2DAT	1.0068
B58C-WTCCC	Affymetrix 500	Chiamo	0.97	0.23 & 0.30	yes	external discordance, relatives,gender discrepancies	0.95	1E-04	0.01	no	IMPUTE	21	35	quicktest	1.0088
B58C-T1DGC	Illumina Infinium 550	Illuminus	0.98	no	yes	external discordance, relatives,gender discrepancies	no	no	no	multi-allelic SNPs, SNPs with mismatch in alleles between dbSNP and Illumina	MACH	21	35	probAbel	1.0125
CHOP	Illumina HH 550v1/v3 HH610	Illumina BeadStudio software	0.98	no	yes, non-cauc excluded	no	0.95	1E-04	0.01	no	Impute	22	36	snptest	1.05
COPSAC	Illumina 550K	BeadStudio v 3.3.4	0.98	no	yes	no	0.95	1E-04	0.01	no	IMPUTE v2	22	36	SNPTEST	1.0272
DNBC	Illumina Human 660w-quad	BeadStudio Genotyping Module, version 3.3.7	0.95	no	yes	no	0.98	0.001	0.01	SNPs where strand issues could not be resolved, e.g., A/T and C/G SNPs	MACH	22	36	MACH2DAT	1.0051
Generation R	Illumina 610K Quad	BeadStudio Genotyping Module, version 3.2.32	0.975	3 SD of the mean	Yes	yes (IBD - check: no family relations)	0.98	1E-06	0.01	no	MACH v1.0.16	22	36	Plink,MACH2DAT	1.0165
GOYA	Illumina 610k		0.95	0.3 & 0.35	MDS	sex discrepancies, related individuals	0.95	1E-07	0.01	NA	MACH	22	36	MACH2DAT	0.9949
KORA F3	Affymetrix 500K	BRLMM	0.93	no	german passport	gender discrepancies	no	no	no	no	IMPUTE		35	snptest	0.9648

KORA F4	Affymetrix Genome-Wide Human SNP Array 6.0	Birdseed2	0.93	no	german passport	gender discrepancies	no	no	no	no	IMPUTE		36	snptest	0.9997
LISA	Affymetrix Genome-Wide Human SNP Array 5.0	BRLMM-P	0.95	no	no	no	0.95	0.01	0.01	no	IMPUTE v1.06	22	36	SNPTEST	1.0223
NFBC66	Illumina HumanCNV370DUO Analysis BeadChip	Beadstudio	0.95	no	no	no phenotype data, IBD, withdrew consent, gender discrepancies, contaminated or duplicate samples	0.95	1E-04	0.01	no	IMPUTE v1.0	21	35	quicktest	1.0097
PIAMA	Illumina Human610 quad array	GenomeStudio Software	0.95	no	no	inconsistent sex	0.95	1E-07	0.01	no	IMPUTE v2	22	36	snptest	1.053
QIMR	Illumina 610K or CNV370	Illumina BeadStudio software	0.95	no	yes	no	0.95	1E-06	0.01	yes (BeadStudio GenCall score <0.7; SNPs exclusive to 610K or CNV370)	MACH	21	35	Plink	0.9968
RAINE	Illumina 660K	Illumina's Bead Studio Genotyping Module software v.3.1	0.95	no	Yes	yes - IBD check and exclude family relations, congenital abnormalities	0.95	5.7E-07	0.01	no	MACH	22	36	MACH2DAT	0.9931
Twins UK	Illumina 317K (3/5) & 610K (2/5)	Illuminus	0.95	Yes	Yes, only caucasian	no	0.95	1E-04	0.01	no	IMPUTE	22	36	Plink	1.0846

(b)

***In silico* replication**

	Genotyping		BEFORE IMPUTATION QUALITY CONTROL PER SUBJECT				BEFORE IMPUTATION QUALITY CONTROL PER SNP				IMPUTATION			DATA ANALYSIS
Cohort	**Genotyping Platform**	**Genotype-Calling Algorithm**	**call rate threshold**	**heterozygosity thresholds**	**ethnicity exclusions**	**other exclusion criteria**	**SNP call rate**	**HWE p-value threshold**	**MAF threshold**	**other exclusion criteria**	**Imputation Software (Version)**	**HapMap CEU Release**	**NCBI Build**	**Association Software**
AAGC	Illumina 610K or CNV370	Illumina BeadStudio software	0.95	no	yes	no	0.95	1E-06	0.01	yes (BeadStudio GenCall score <0.7; SNPs exclusive to 610K or CNV370)	Impute2	1000 Genomes Project (CEU Mar 2010) + HapMap3 (All 11 populations, Feb 2009)	36	Plink
ALSPAC	Illumina HumanHap550 quad		0.97	0.32 - 0.345 or 0.31 - 0.33	caucasians only	sex discrepancies, cryptic relatedness, replicates <80% IBD	0.95	5E-07	0.01	No	Mach 1.0.16	22	36	Mach2Dat
BAMSE*	illumina 610k	GenCall	no	no	caucasians only	sex discrepancies, related individuals	no	no	no	No	Mach	22	36	ProbAbel
B58C-REPL	Illumina 550k/610k	GenCall	0.98	none	yes	none	0.95	1E-04	0.01	inconsistency of allele frequency across multple deposits	Mach	21	35	ProbAbel
ECRHS*	illumina 610 quad	Gencall	no	no	caucasians only	sex discrepancies, cryptic relatedness	no	no	no	no	MACH	22	36	ProbABEL
Generation R	Illumina 610K quad	BeadStudio Genotyping Module, version 3.2.32	0.975	3 SD of the mean	Yes	yes (IBD - check: no family relations)	0.98	1E-06	0.01	no	MACH v1.0.16	22	36	Plink, MACH2DAT
LISA/GINI	Affymetrix 5.0 Affymetrix 6.0	BRLMM-P (5.0), BIRDSEED V2 (6.0)	0.95	Mean +/- 4 SD	caucasians only	sex discrepancies	0.95	1E-5	0.01	no	Impute2	22	36	SnpTest

MAAS	illumina 610 quad	Illumina GenCall application	0.97	outliers	caucasians only	sex discrepancies, were non-concordant on sequenome genotyping	0.95	5.9E-07	0.01	No	Impute2	3 + 1000 genomes	36	SnpTest
MoBa	illumina 610 quad	Gen Call	0.97			sex discrepancies	0.95	1E-03	0.01		Plink	22	36	Plink
NTR	Affymetrix 6.0	Birdseed V2	no	no	no	Clear sample switches based on fingerprint data (64 SNPs)	0.95	1E-04	0.01	MI>35	Beagle	22	36	Plink
SAPALDIA*	illumina 610 quad	Gencall	no	no	caucasians only	sex discrepancies, cryptic relatedness	no	no	no	no	Mach	22	36	ProbABEL

***de novo* genotyping replication**

			QUALITY CONTROL PER SUBJECT			QUALITY CONTROL PER SNP		
Cohort	**Genotyping Method**	**Genotype-Calling Algorithm**	**call rate threshold**	**ethnicity exclusions**	**other exclusion criteria**	**lowest SNP call rate**	**SNPs with HWE p-values <0.05**	**Association Software**
Health2006	The PCR KASPar genotyping system (KBiosciences, Hoddesdon, UK).	Kraken (Kbioscience)	0.98	caucasians	Danish citizenship, born in Denmark	0.98	0	SPSS
KORA F4 / GENEVA	Sequenom MALDI-TOF MS 4.0	Sequenom Typer 4.0	0.97	caucasian	sex discrepancies	0.97	0	R
NFBC86	The PCR KASPar genotyping system (KBiosciences, Hoddesdon, UK).	Klustercaller (Kbioscience)	0.97			0.97	0	Quicktest

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*GABRIEL cohorts had QC applied only after the imputation step, see BAMSE methods for details.

Supplementary Table 3. Discovery and replication results of the top 11 SNPs for atopic dermatitis. 1 SNP per region was followed up in the replication stage. Results are for the fixed effect inverse-variance meta-analysis, with genomic control applied to the individual studies in the discovery meta-analysis. The heterogeneity p-value (het p), testing for overall heterogeneity between all discovery and replication studies was generated using Cochran's Q-test for heterogeneity. All OR (odds ratios) are given with the minor allele representing the effect allele (Eff). CI denotes the confidence interval

				Alleles		Discovery				Replication			Combined			
chr	SNP	Position (bp)	Gene	Eff	Alt	Effect Allele Freq	N	OR (95% CI)	pvalue	N	OR (95% CI)	pvalue	N	OR(95%CI)	pvalue	het p
11	rs479844	65308533	OVOL1	A	G	0.44	26,151	0.89 (0.85, 0.93)	**7.8E-07**	25,098	0.87 (0.83,0.92)	**2.4E-08**	51,249	0.88 (0.85,0.91)	**1.1E-13**	0.23
19	rs2164983	8650381	ACTL9	A	C	0.15	17,403†	1.22 (1.13, 1.32)	**1.8E-07**	22,996	1.11 (1.04,1.19)	**0.002**	40,399	1.16 (1.10,1.22)	**7.1E-09**	0.004
1	rs9050*	150345938	TCHH	A	C	0.06	25,788	1.33 (1.20, 1.47)	**1.9E-08**	-	-	-	-	-	-	0.95
5	rs2897442	132076926	KIF3A	C	T	0.29	26,164	1.12 (1.07, 1.18)	**7.8E-06**	25,064	1.09 (1.04,1.15)	**0.001**	51,228	1.11 (1.07,1.15)	**3.8E-08**	0.52
8	rs7000782	81470705	ZBTB10	A	T	0.43	26,077	1.14 (1.09, 1.20)	**1.6E-08**	20,873	1.03 (0.98,1.08)	**0.296**	46,950	1.09 (1.05,1.13)	**1.1E-06**	0.24
22	rs4821544	35588449	NCF4	C	T	0.29	24,770	1.13 (1.07, 1.19)	**3.5E-06**	25,103	1.05 (0.99,1.10)	**0.077**	49,873	1.09 (1.05,1.13)	**5.5E-06**	0.53
6	rs3853601	31607582	BAT1	G	C	0.12	25,528	1.17 (1.09, 1.26)	**7.6E-06**	21,964	1.09 (1.01,1.17)	**0.031**	47,492	1.13 (1.08,1.19)	**1.9E-06**	0.04
10	rs10994675	51233999	MSMB	A	G	0.42	24,787	1.12 (1.07, 1.17)	**3.1E-06**	22,903	1.00 (0.95,1.05)	**0.929**	47,690	1.06 (1.03,1.10)	**0.001**	0.39
13	rs1327914	95891570	HS6ST3	C	T	0.17	26,168	1.16 (1.10, 1.24)	**8.9E-07**	25,088	0.98 (0.92,1.04)	**0.434**	51,256	1.07 (1.02,1.12)	**0.003**	0.005
10	rs4520482	67139368	CTNNA3	A	G	0.43	26,031	0.90 (0.86, 0.94)	**8.7E-06**	25,109	1.02 (0.97,1.07)	**0.457**	51,140	0.96 (0.92,0.99)	**0.008**	0.32
9	rs10983837	119738636	TLR4	A	C	0.03	26,101	1.35 (1.18, 1.54)	**6.8E-06**	24,168	0.92 (0.80,1.05)	**0.229**	50,269	1.12 (1.02,1.24)	**0.015**	0.002

*rs9050 (and other associated SNP rs11205006 in the same region) were excluded from the replication phase after they were found to not be independent from the association with the *FLG* mutations in the same region.

†rs2164983 was not included in the HapMap release 21 and so was missing for some discovery cohorts.

The SNP rs1327914 was replaced by the SNP rs927709 (r^2=1.00) in the B58C-WTCCC, B58C-T1DGC, KORA-F3, NFBC66 and the B58C replication cohort

Supplementary Table 4. AD association results from the discovery meta-analysis for the 15 loci associated with asthma or total serum IgE levels in a recent GWAS. 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.

					Moffat et al. (2010) asthma association results		AD association results from current meta-analysis	
SNP	**Gene**	**Position**	**effect allele**	**other allele**	**OR (95% CI)**	**pvalue**	**OR (95% CI)**	**pvalue**
rs3771166	*IL18R1*	2q12.1	a	g	0.87 (0.83-0.91)	3.4E-09	1.00 (0.95-1.05)	0.9791
rs9273349	*HLA-DQB1*	6p21.32	g	a	1.18 (1.13-1.24)	7.0E-14	0.95 (0.86-1.04)	0.2647
rs1342326	*IL33*	9p24.1	c	a	1.20 (1.13-1.28)	9.2E-10	0.99 (0.93-1.05)	0.7789
rs744910	*SMAD3*	15q22.33	a	g	0.89 (0.86-0.92)	3.9E-09	0.98 (0.94-1.03)	0.3987
rs2305480	*GSDMB*	17q12	a	g	0.85 (0.81-0.90)	9.6E-08	1.00 (0.96-1.05)	0.8723
rs3894194	*GSDM1*	17q21.1	a	g	1.17 (1.11-1.23)	4.6E-09	1.00 (0.95-1.04)	0.8893
rs2284033	*IL2RB*	22q12.3	a	g	0.89 (0.86-0.93)	1.1E-08	1.03 (0.98-1.07)	0.2845
rs1295686	*IL13*	5q31.1	c	t	0.85 (0.79-0.90)	1.4E-07	0.91 (0.86-0.96)	0.0008
rs2073643	*SLC22A5*	5q31.1	c	t	0.89 (0.84-0.93)	2.2E-07	0.96 (0.92-1.00)	0.0771
rs11071559	*RORA*	15q22.2	t	c	0.88 (0.81-0.95)	1.1E-07	1.01 (0.95-1.08)	0.7475

					Moffat et al. (2010) total serum IgE association results		AD association results from current meta-analysis	
SNP	**Gene**	**Position**	**effect allele**	**other allele**	**beta**	**pvalue**	**OR (95% CI)**	**pvalue**
rs2252226	*FCER1A*	1q23.2	t	c	NA	6.6E-05	0.96 (0.92-1.01)	0.0817
rs20541	*IL13*	5q31.1	a	g	NA	1.0E-06	1.10 (1.04-1.16)	0.0007
rs9271300	*HLA-DRB1*	6p21.32	c	g	NA	8.3E-15	0.99 (0.90-1.09)	0.9013
rs167769	*STAT6*	12q13.3	t	c	NA	8.5E-07	1.05 (1.00-1.10)	0.0379
rs1859308	*IL4-R/IL21R*	16p12.1	a	g	NA	8.2E-06	0.97 (0.91-1.04)	0.4477

Supplementary Table 5. Meta-analysis results for interactions between the three identified loci. Results are based on the discovery cohorts. Betas are the ln(odds) of AD per 1 unit change in the interaction variable (SNP1*SNP2, SNPs coded as 0,1,2 with the minor allele as the increasing allele).

Interaction	beta	95% CI	p-value
rs2897442*rs479844	-0.020	-0.090 to 0.050	0.578
rs2897442*rs2164983	0.038	-0.081 to 0.157	0.535
rs2164983*rs479844	0.019	-0.086 to 0.124	0.722

Supplementary Table 6. Immunochip association results on region 5q31.1. Conditional association analysis for markers of the cytokine cluster on 5q31.1 including *IL13* polymorphisms previously shown to be associated with asthma and psoriasis risk, as well as the GWAS *KIF3A* polymorphism showing the strongest association in the meta-analysis and the lead SNP of the corresponding putative LD-block from the finemapping approach.

		Marker 1				
		rs1800925 (IL13)	rs20541 (IL13)	rs848 (IL13)	rs66913936 (IL4)	rs2897442 (KIF3A)
Marker 2	rs1800925 (IL13)	***1.32 (1.20-1.46)*** ***P=1.74 x 10^{-8}***	1.26 (1.11-1.41) P=0.0002	1.27 (1.12-1.42) P=0.0001	1.23 (1.11-1.35) P=5.36 x 10^{-5}	1.19 (1.08-1.31) P=0.0005
	rs20541 (IL13)	1.17 (1.04-1.32) P=0.0085	***1.37 (1.24-1.52)*** ***P=4.07 x 10^{-10}***	1.42 (0.72-2.81) P=0.3090	1.18 (1.06-1.31) P=0.0018	1.14 (1.03-1.26) P=0.0096
	rs848 (IL13)	1.17 (1.04-1.31) P=0.0107	0.97 (0.49-1.92) P=0.9249	***1.38 (1.25-1.52)*** ***P=1.93 x 10^{-10}***	1.18 (1.06-1.31) P=0.0022	1.14 (1.03-1.26) P=0.0113
	rs66913936 (IL4)	1.24 (1.12-1.37) P=3.53 x 10^{-5}	1.27 (1.13-1.42) P=2.86 x 10	1.28 (1.14-1.42) P=1.74 x 10^{-5}	***1.31 (1.19-1.43)*** ***P=2.58 x 10^{-8}***	0.91 (0.71-1.17) P=0.4742
	rs2897442 (KIF3A)	1.26 (1.14-1.39) P=1.01 x 10^{-5}	1.29 (1.16-1.44) P=3.42 x 10^{-6}	1.30 (1.17-1.45) P=2.00 x 10^{-6}	1.43 (1.10-1.84) P=0.0069	***1.26 (1.15-1.38)*** ***P=8.84 x 10^{-7}***

Conditional analysis of Marker 1 conditioned on Marker 2 using the logistic regression framework. The diagonal elements shows results of the unconditional analysis. Displayed are odds ratios with corresponding 95% confidence intervals in brackets and P-values

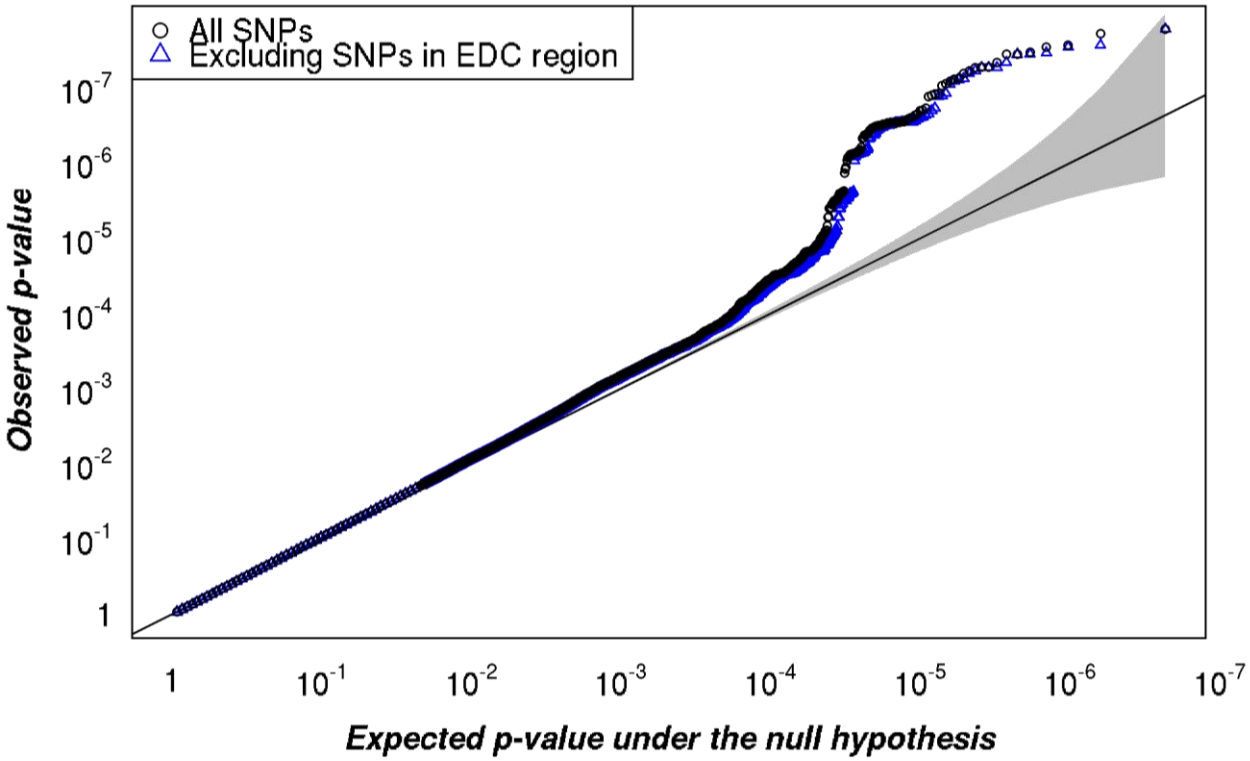
Supplementary Table 7. Immunochip linkage disequilibrium (LD) in region 5q31.1. Pair-wise LD measures between markers of the cytokine cluster on 5q31.1 including *IL13* polymorphisms previously shown to be associated with asthma and psoriasis risk, as well as the GWAS KIF3A polymorphism showing the strongest association in the meta-analysis and the lead SNP of the corresponding putative LD-block from the finemapping approach.

				Marker 1		
Marker 2		rs1800925 (IL13)	rs20541 (IL13)	rs848 (IL13)	rs66913936 (IL4)	rs2897442 (KIF3A)
	rs1800925 (IL13)	1	0.301	0.298	0.090	0.078
	rs20541 (IL13)	0.564	1	0.979	0.192	0.164
	rs848 (IL13)	0.558	0.995	1	0.194	0.166
	rs66913936 (IL4)	0.328	0.493	0.492	1	0.858
	rs2897442 (KIF3A)	0.323	0.483	0.483	0.982	1

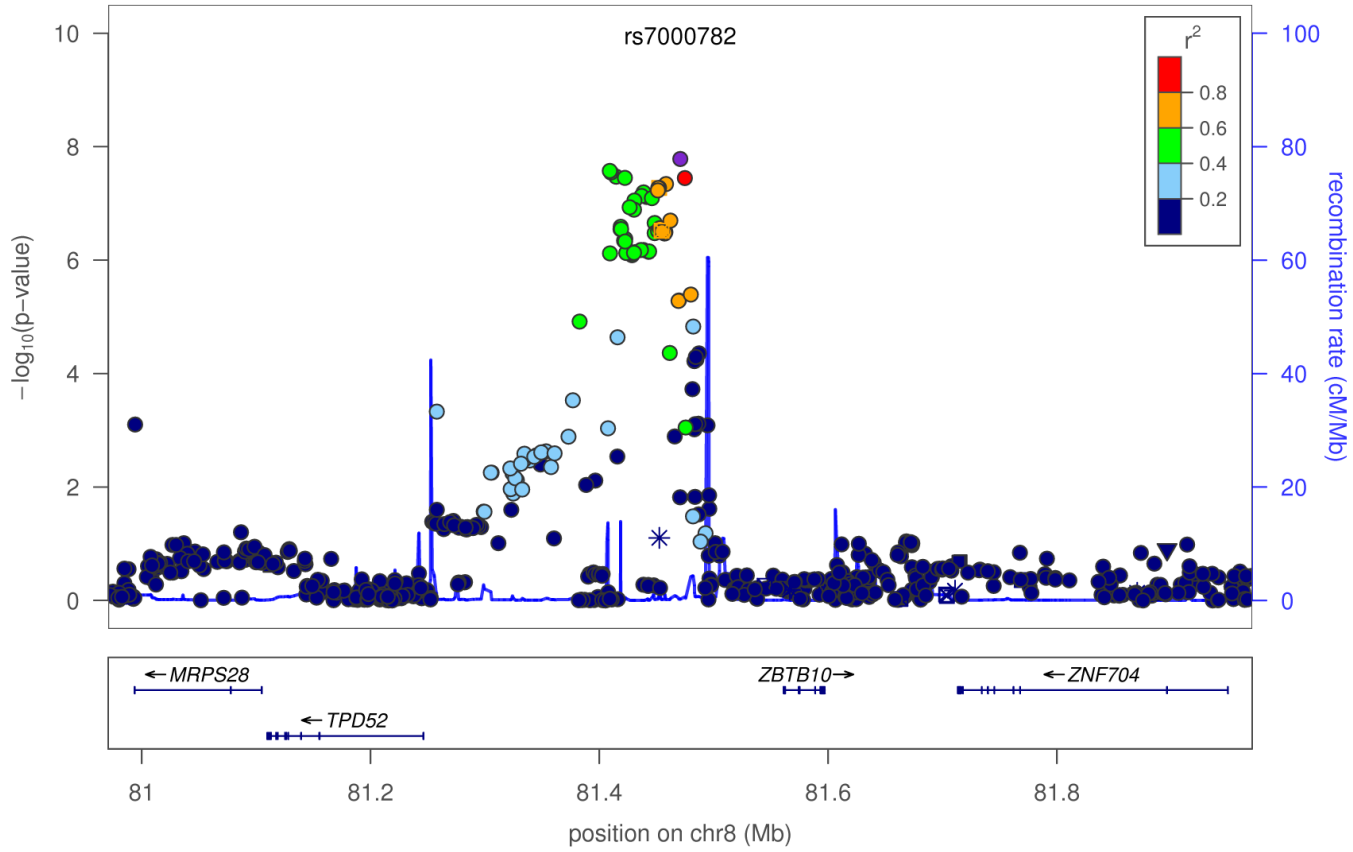
The upper triangular matrix shows r^2 values, whereas the lower triangular matrix displays D' values. The color coding refers to the strength of LD.

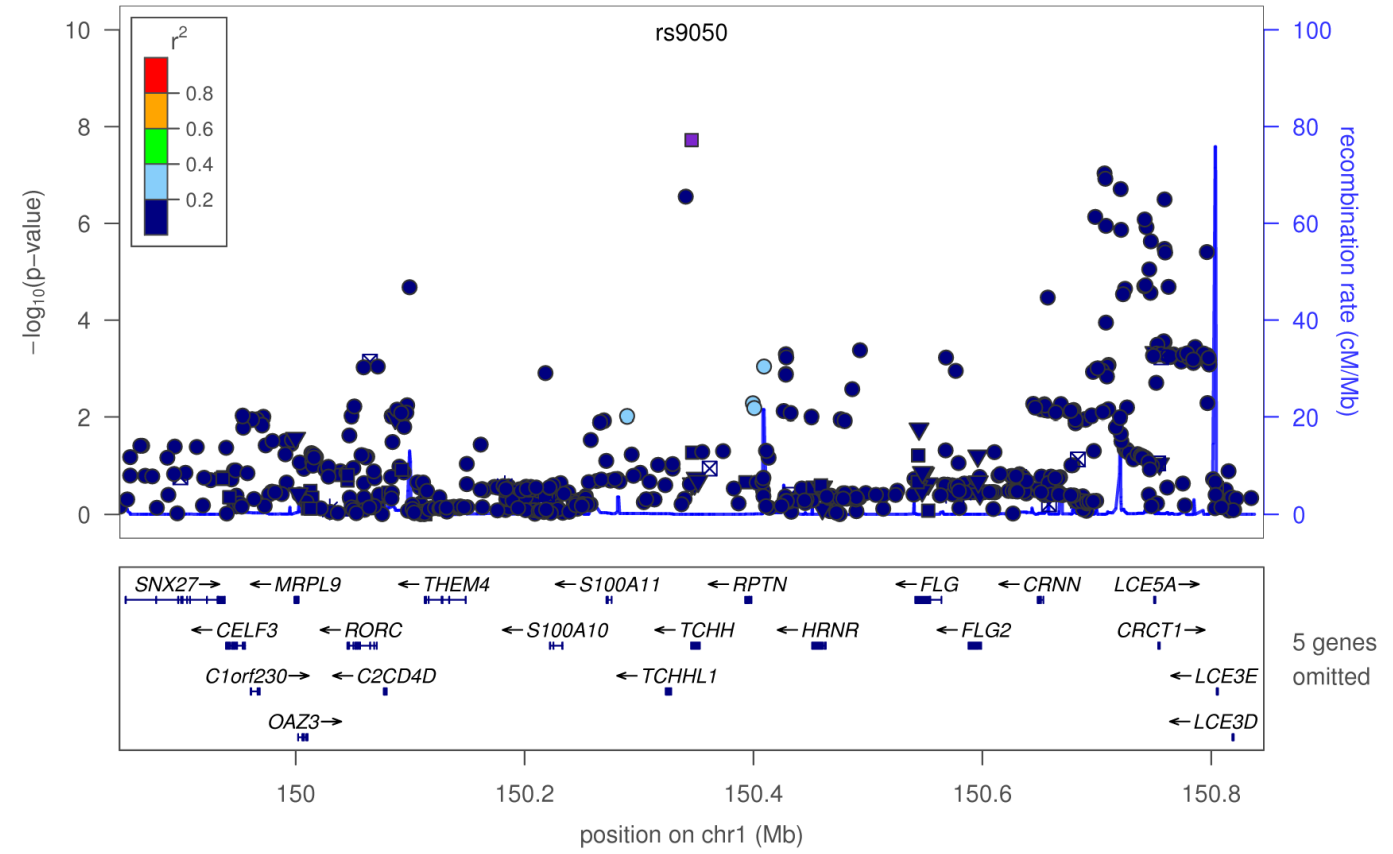
Values	R^2	D'
<0.2		
0.2-0.4		
0.4-0.6		
0.6-0.8		
>0.8		

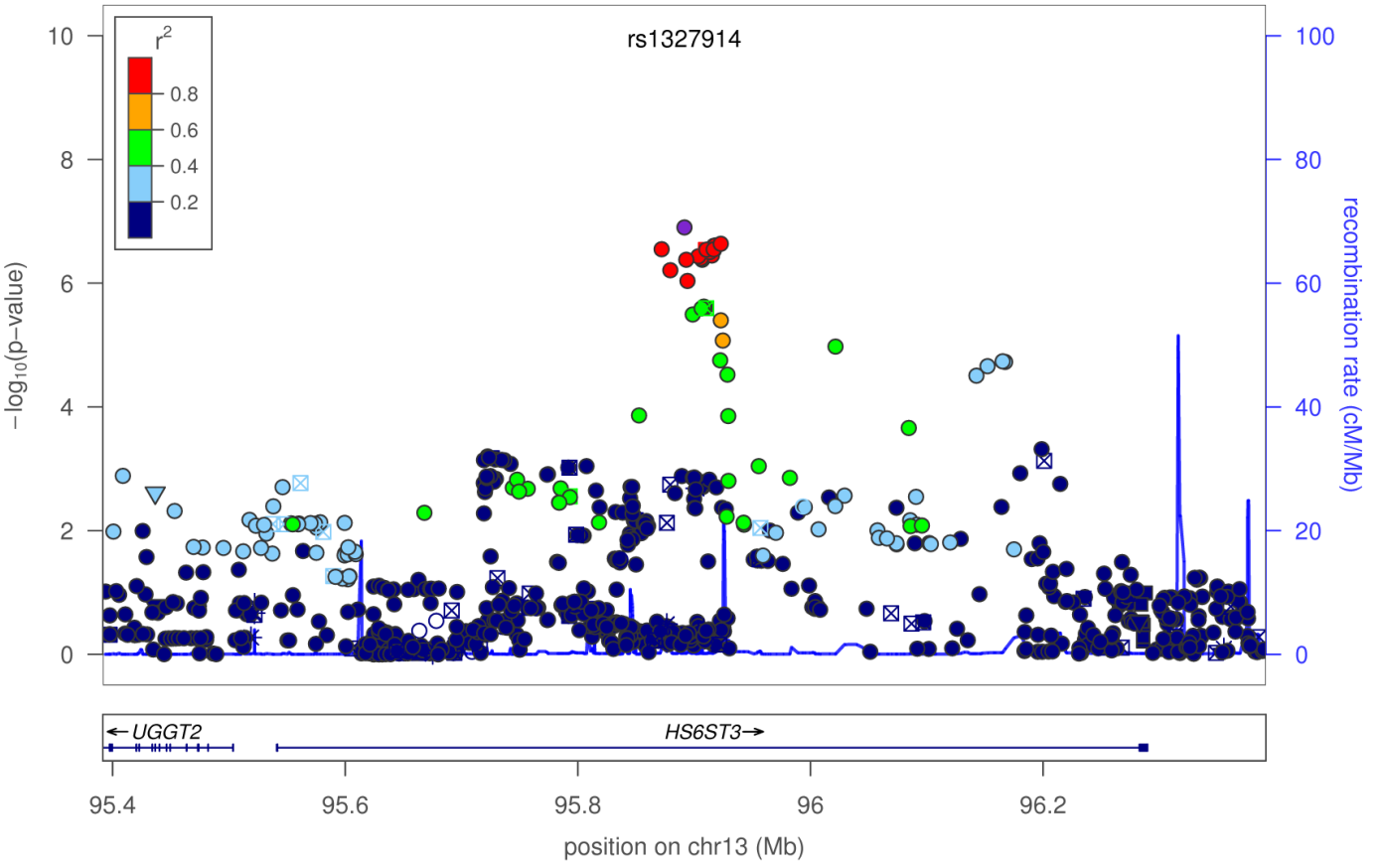
Supplementary Figure 1. QQ plot for the discovery genome-wide association meta-analysis, after excluding all SNPs MAF<1% and Rsqr<0.3 or proper_info<0.4. □=1.017.EDC=epidermal differentiation complex region (which contains FLG) defined as Chr 1:150.2-151.9Mb.

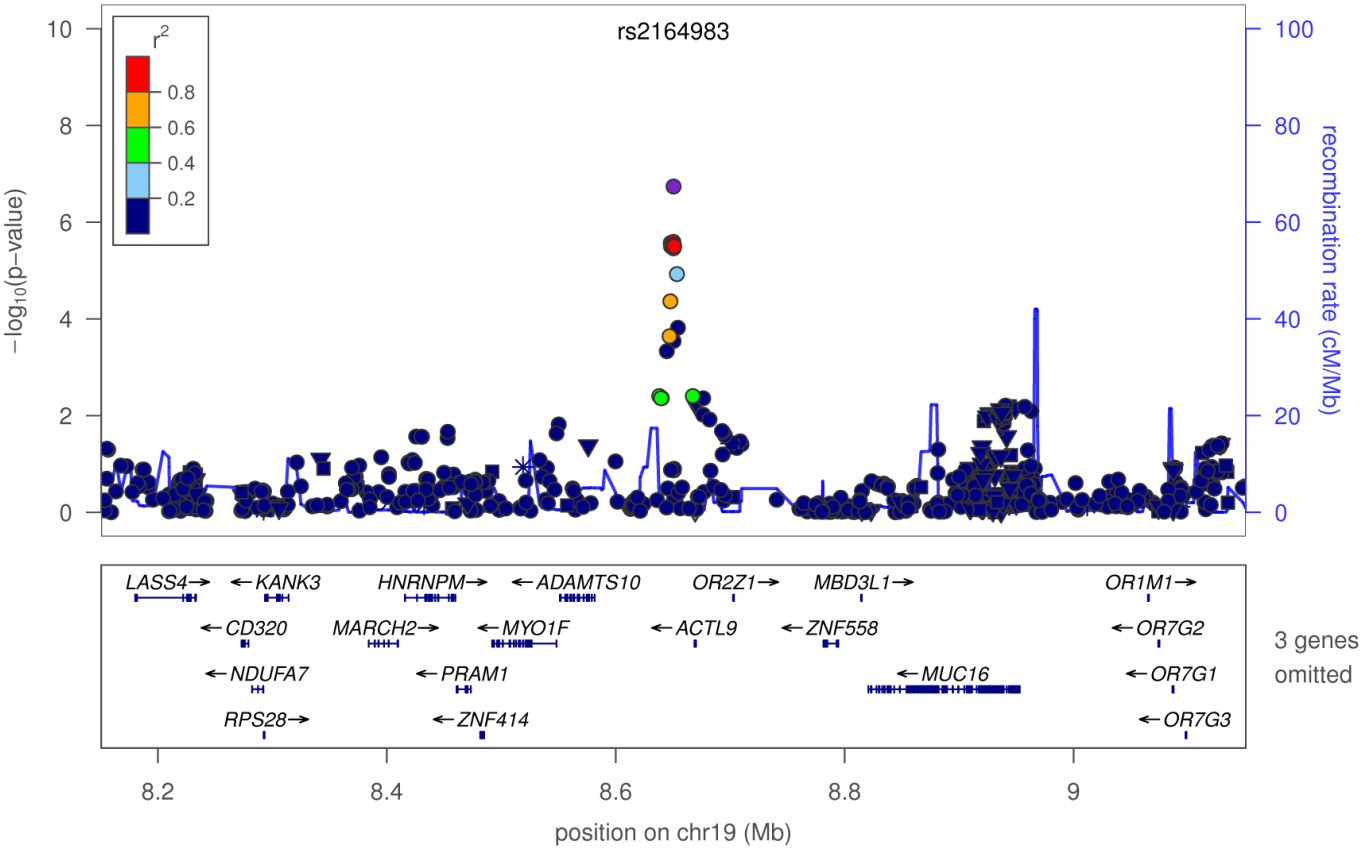


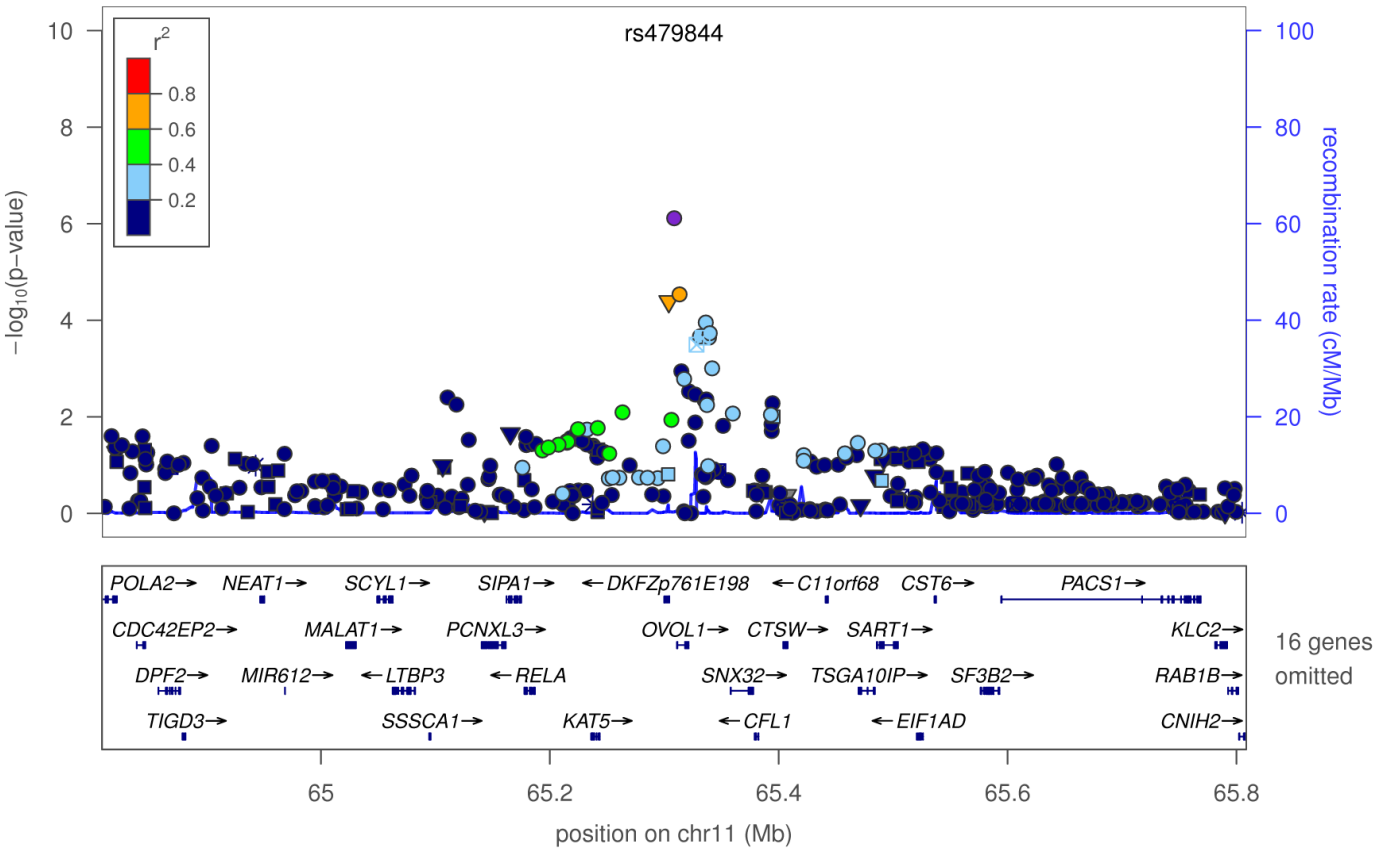
Supplementary Figure 2. Regional association plots for the top 11 regions. Ordered by significance in the discovery analysis.

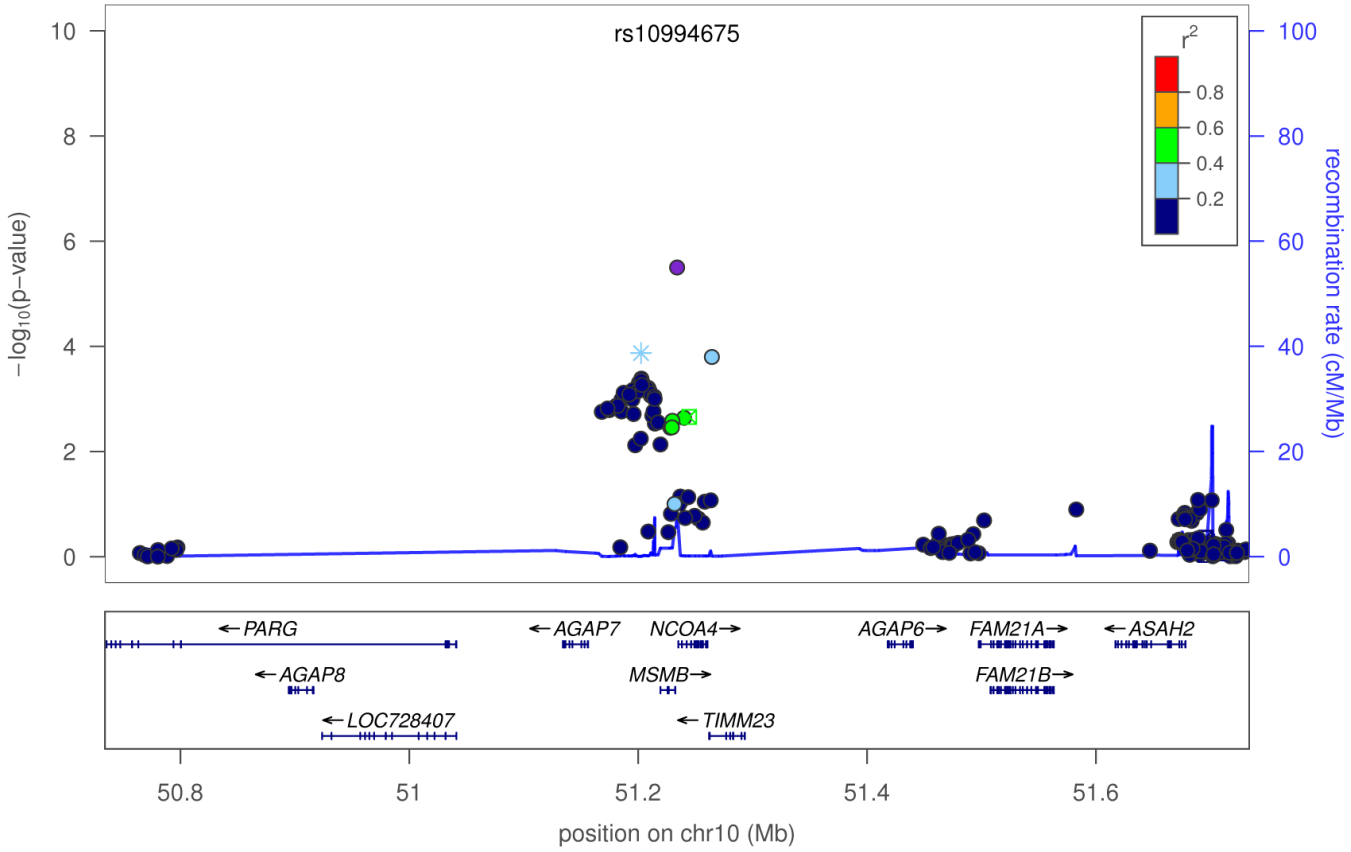


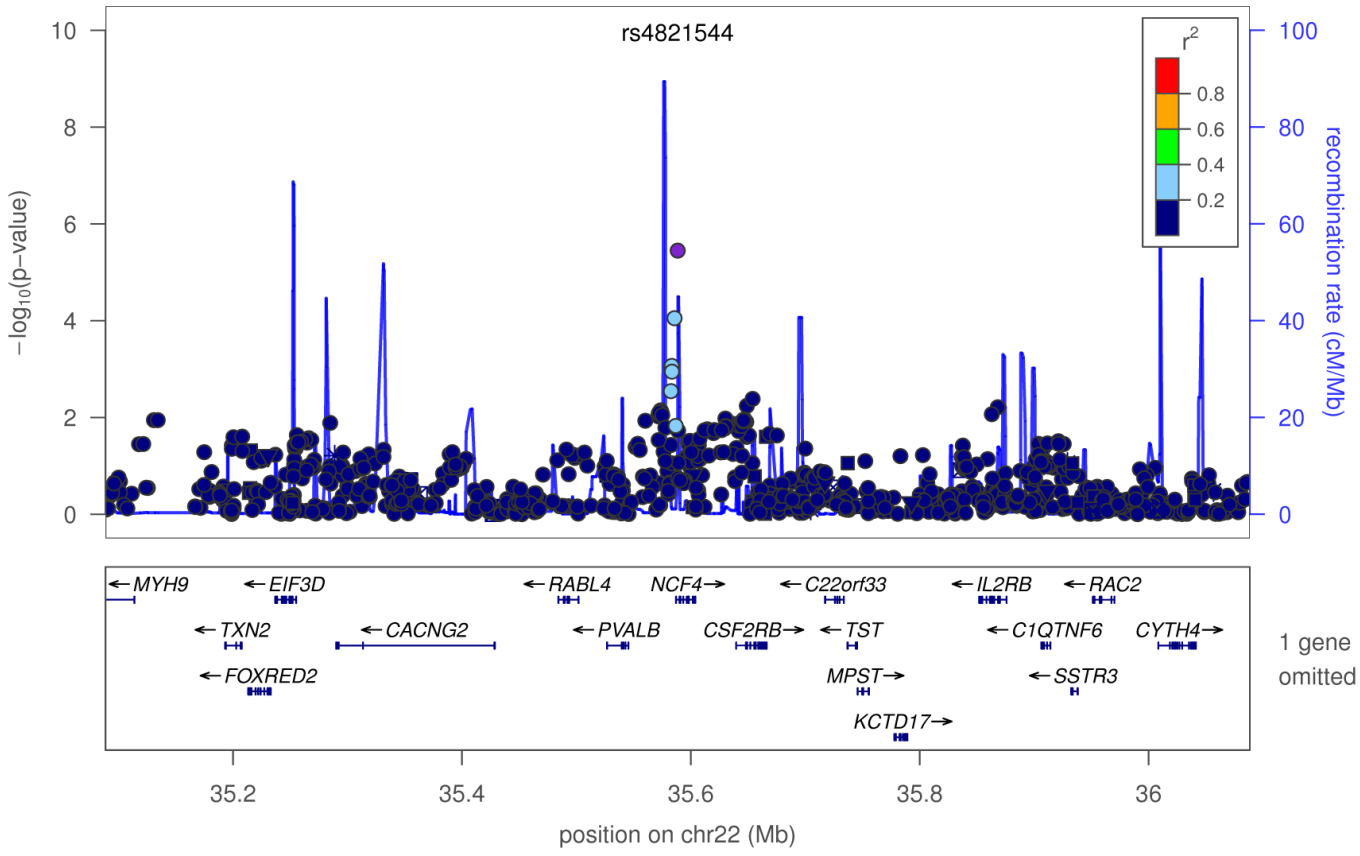

rs9050
r²
0.8
0.6
0.4
0.2
−log10(p−value)
recombination rate (cM/Mb)
SNX27→
←MRPL9
←THEM4
←S100A11
←RPTN
←FLG
←CRNN
LCE5A→
←CELF3
←RORC
←S100A10
←TCHH
←HRNR
←FLG2
CRCT1→
C1orf230→
←C2CD4D
←TCHHL1
←LCE3E
OAZ3→
←LCE3D
5 genes omitted
150
150.2
150.4
150.6
150.8
position on chr1 (Mb)

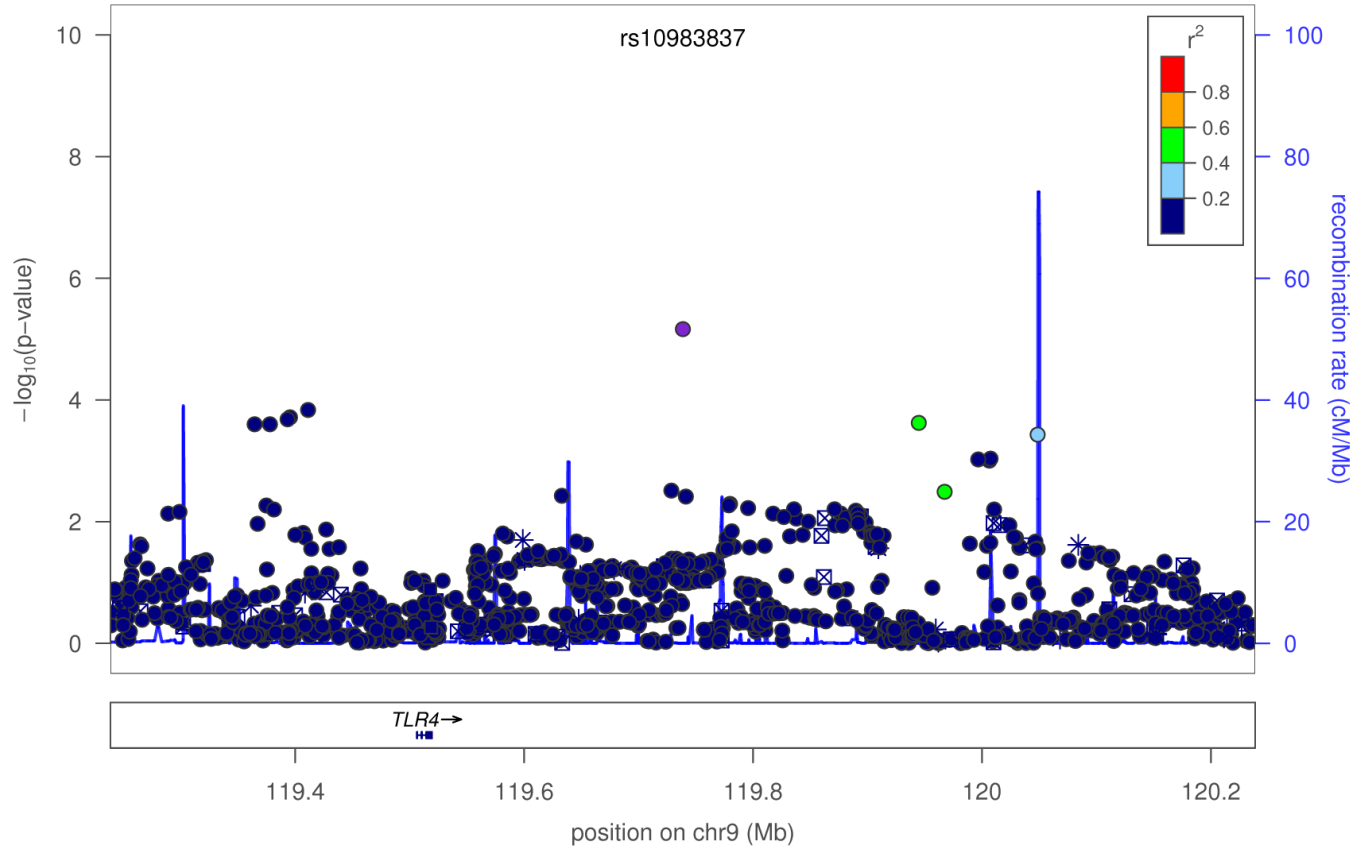

rs1327914
r²
0.8
0.6
0.4
0.2
−log10(p−value)
recombination rate (cM/Mb)
←UGGT2
HS6ST3→
95.4
95.6
95.8
96
96.2
position on chr13 (Mb)

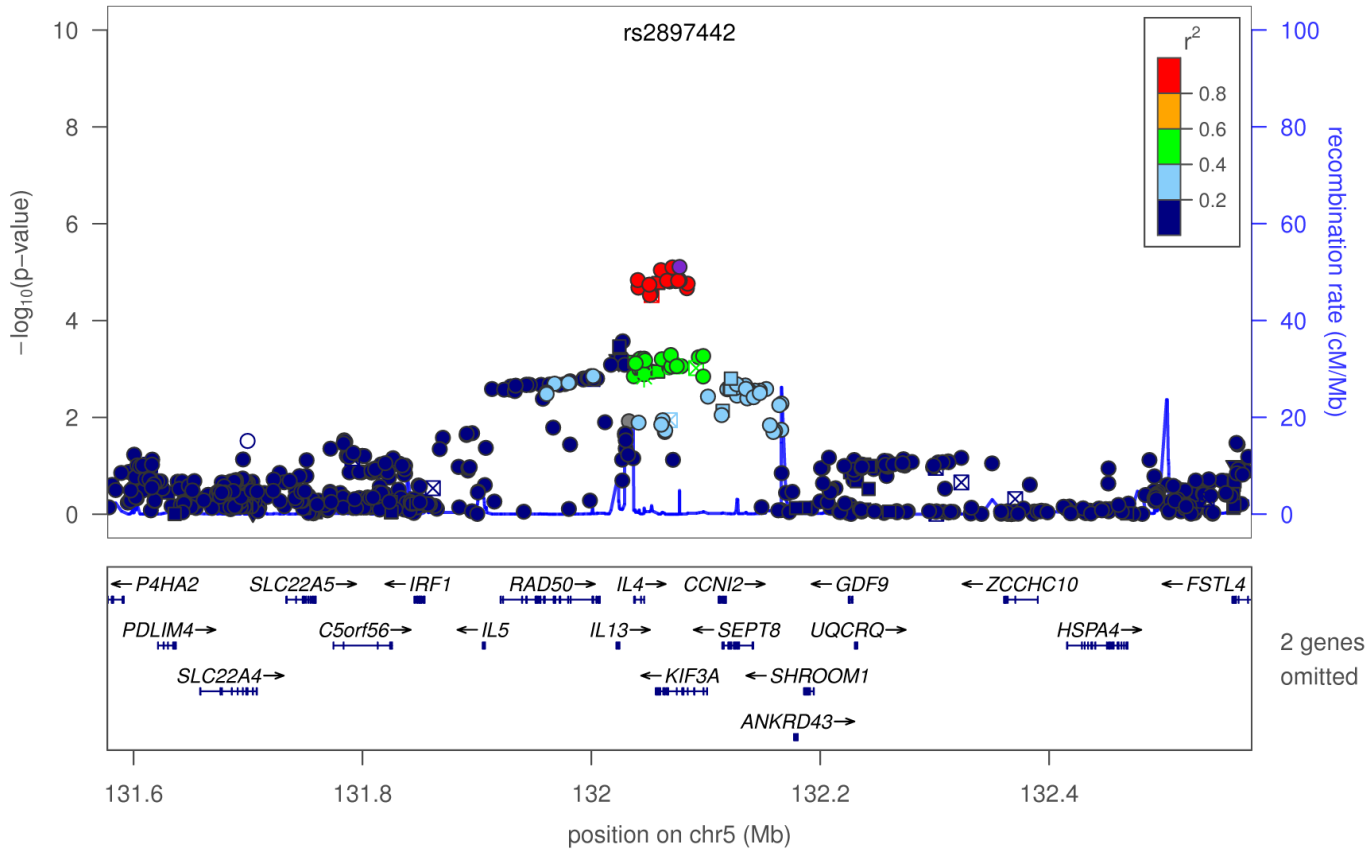

rs2164983
r²
0.8
0.6
0.4
0.2
−log10(p−value)
recombination rate (cM/Mb)
LASS4→ ←KANK3 HNRNPM→ ←ADAMTS10 OR2Z1→ MBD3L1→ OR1M1→
←CD320 MARCH2→ ←MYO1F ←ACTL9 ←ZNF558 ←OR7G2
←NDUFA7 ←PRAM1 ←MUC16 ←OR7G1
RPS28→ ←ZNF414 ←OR7G3
3 genes omitted
position on chr19 (Mb)

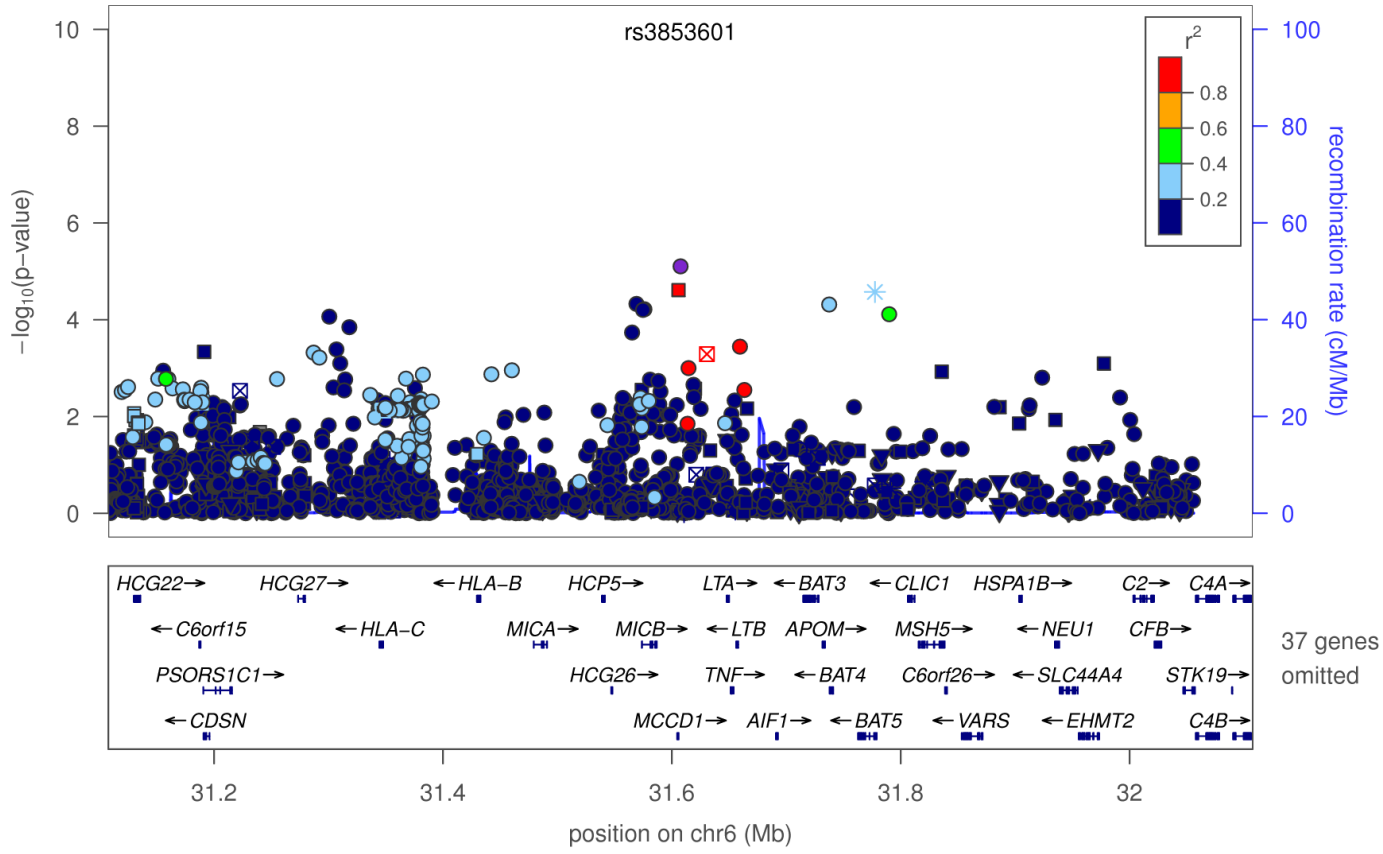

rs479844
r²
0.8
0.6
0.4
0.2
−log10(p−value)
recombination rate (cM/Mb)
POLA2→ NEAT1→ SCYL1→ SIPA1→ ←DKFZp761E198 ←C11orf68 CST6→ PACS1→
CDC42EP2→ MALAT1→ PCNXL3→ OVOL1→ CTSW→ SART1→ KLC2→
DPF2→ MIR612→ ←LTBP3 ←RELA SNX32→ TSGA10IP→ SF3B2→ RAB1B→
TIGD3→ SSSCA1→ KAT5→ ←CFL1 ←EIF1AD CNIH2→
16 genes omitted
position on chr11 (Mb)

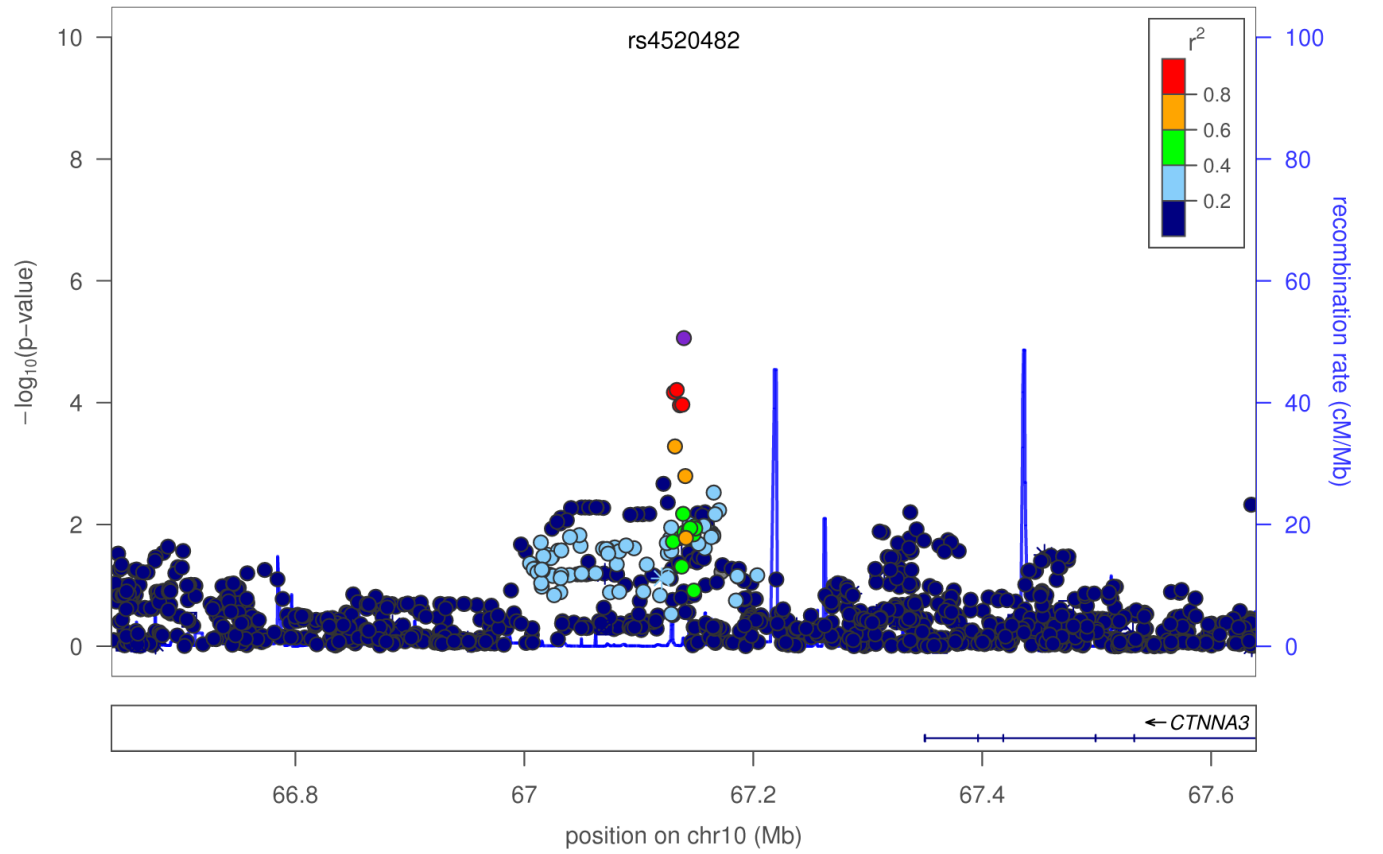

rs10994675
r²
0.8
0.6
0.4
0.2
−log10(p−value)
recombination rate (cM/Mb)
PARG
AGAP7
NCOA4
AGAP6
FAM21A
ASAH2
AGAP8
MSMB
FAM21B
LOC728407
TIMM23
50.8
51
51.2
51.4
51.6
position on chr10 (Mb)


rs4821544
r²
0.8
0.6
0.4
0.2
−log10(p−value)
recombination rate (cM/Mb)
MYH9
EIF3D
RABL4
NCF4
C22orf33
IL2RB
RAC2
TXN2
CACNG2
PVALB
CSF2RB
TST
C1QTNF6
CYTH4
FOXRED2
MPST
SSTR3
KCTD17
1 gene
omitted
35.2
35.4
35.6
35.8
36
position on chr22 (Mb)


rs10983837
r²
0.8
0.6
0.4
0.2
−log10(p−value)
recombination rate (cM/Mb)
TLR4
119.4
119.6
119.8
120
120.2
position on chr9 (Mb)

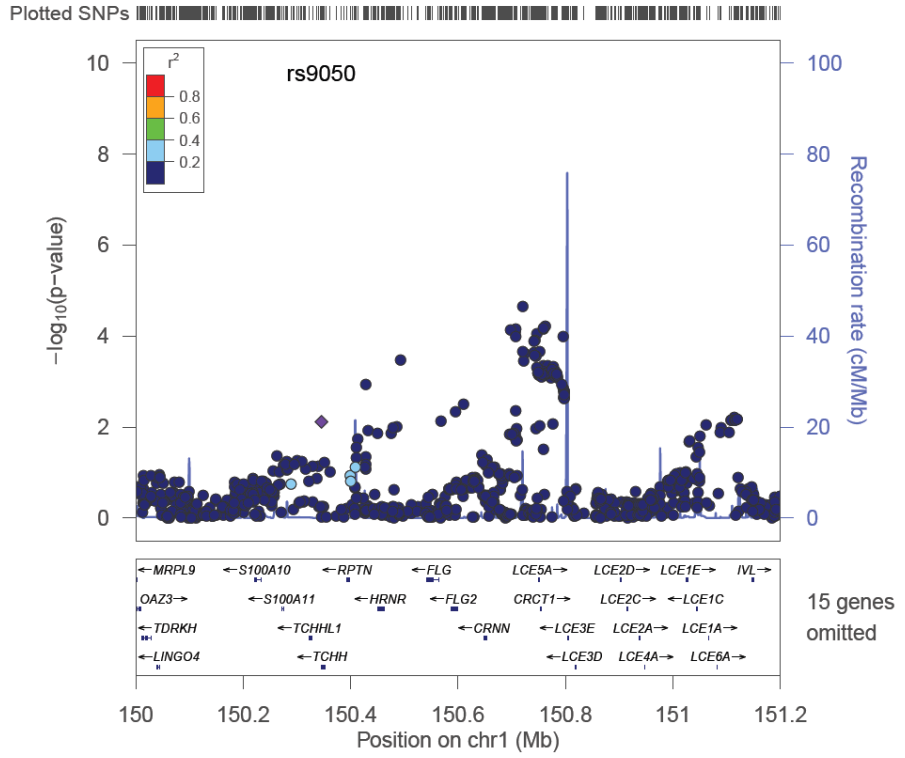

rs2897442
r²
0.8
0.6
0.4
0.2
−log10(p−value)
recombination rate (cM/Mb)
P4HA2
SLC22A5
IRF1
RAD50
IL4
CCNI2
GDF9
ZCCHC10
FSTL4
PDLIM4
C5orf56
IL5
IL13
SEPT8
UQCRQ
HSPA4
SLC22A4
KIF3A
SHROOM1
ANKRD43
2 genes omitted
131.6
131.8
132
132.2
132.4
position on chr5 (Mb)


rs3853601
r²
0.8
0.6
0.4
0.2
−log10(p−value)
recombination rate (cM/Mb)
HCG22→ HCG27→ ←HLA−B HCP5→ LTA→ ←BAT3 ←CLIC1 HSPA1B→ C2→ C4A→
←C6orf15 ←HLA−C MICA→ MICB→ ←LTB APOM→ MSH5→ ←NEU1 CFB→
PSORS1C1→ HCG26→ TNF→ ←BAT4 C6orf26→ ←SLC44A4 STK19→
←CDSN MCCD1→ AIF1→ ←BAT5 ←VARS ←EHMT2 C4B→
37 genes omitted
position on chr6 (Mb)

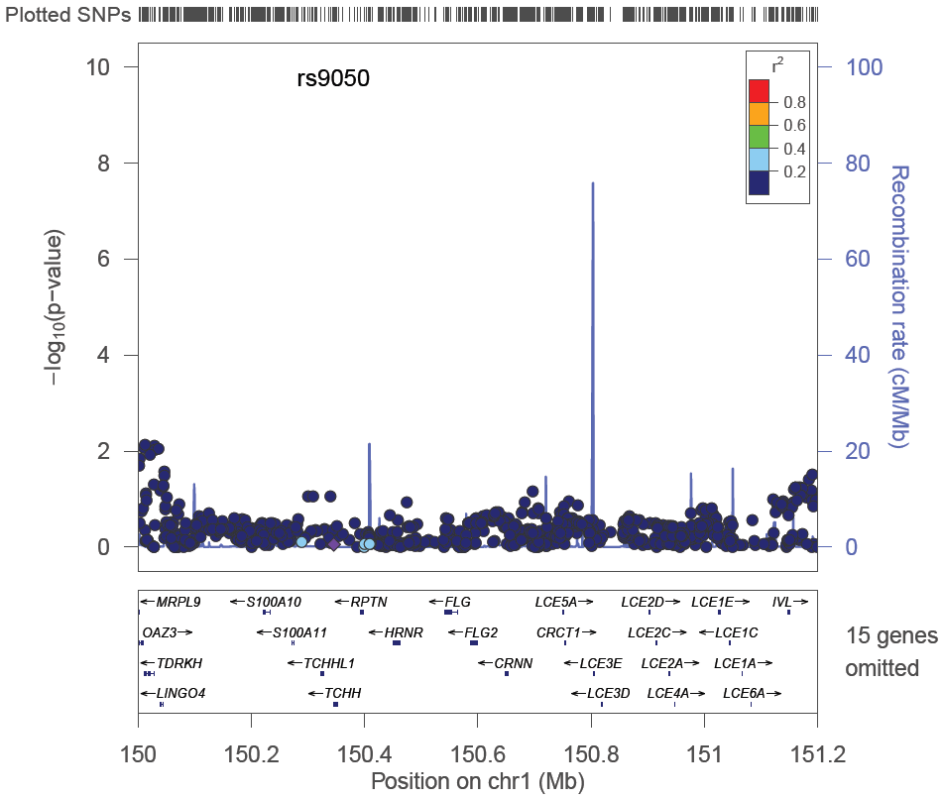

rs4520482
r²
0.8
0.6
0.4
0.2
−log10(p−value)
recombination rate (cM/Mb)
←CTNNA3
position on chr10 (Mb)

Supplementary Figure 3. Meta-analysis of 8 studies with no adjustment for FLG mutations (a) and with adjustment for FLG R501X and 2282del4 mutations (b). rs9050 (purple diamond) OR=1.28, p-value=0.008 in (a) and OR=0.98, p-value=0.88 in (b). A second SNP in the region (rs11205006 at ~150.7Mb) OR=1.21, p-value=8x10^{-5} in (a) and OR=1.09, p-value=0.15 in (b). Plotted using LocusZoom (csg.sph.umich.edu/locuszoom/). Data from ALSPAC, BAMSE, COPSAC, KORA F3, KORA F4, LISA, MAAS and PIAMA studies contributed to these analyses.

a.

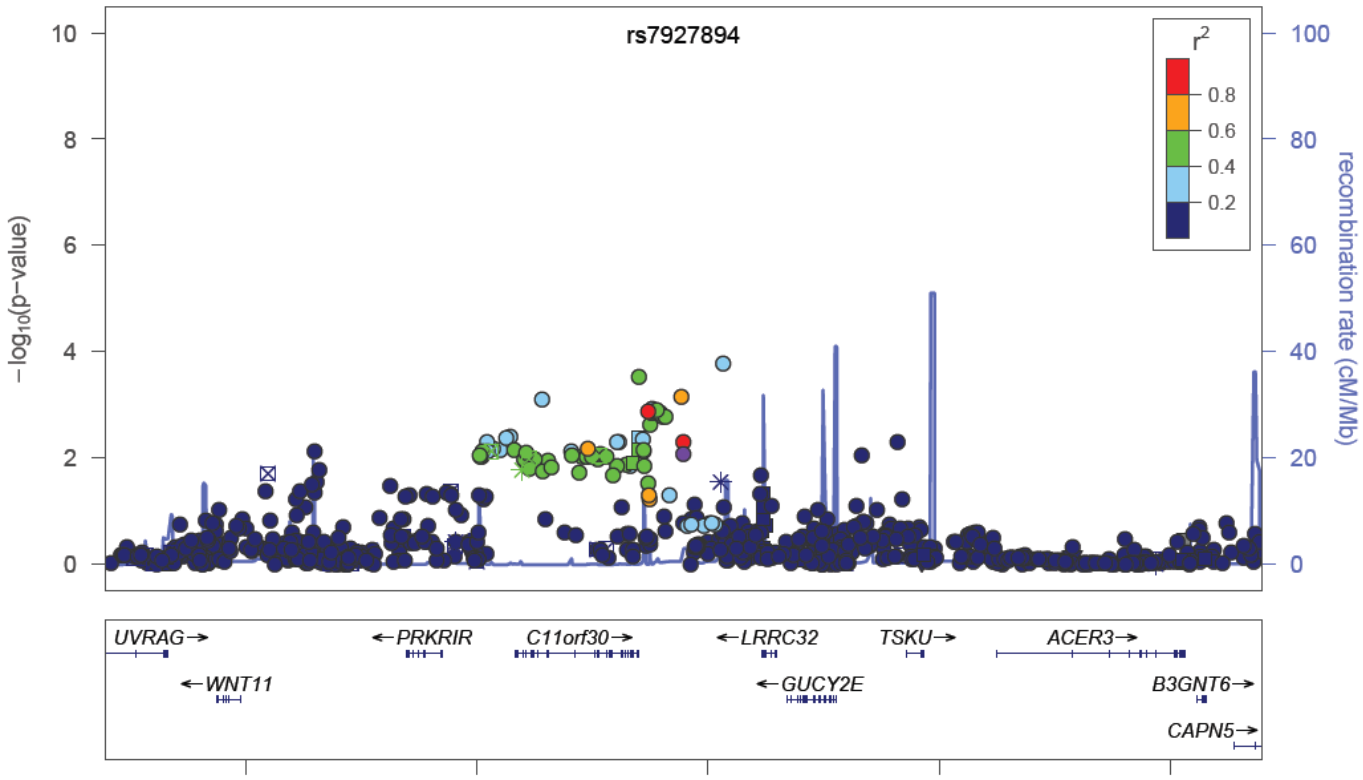


b.

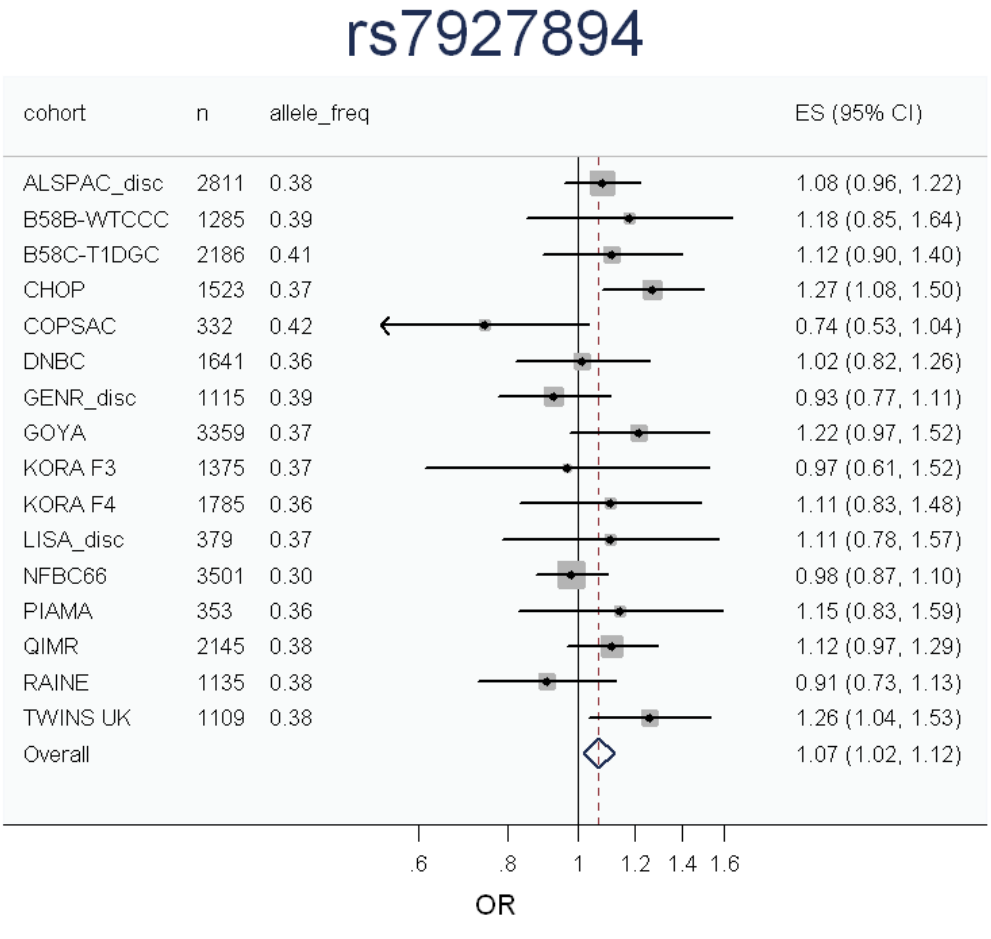


Supplementary Figure 4. Previously known 11q13 (rs7927894) association in our study. (a) The regional association plot for the discovery meta-analysis (top SNP, rs11236810 p=0.0002**),** (b) The forest plot for the association in each of the discovery cohorts for rs7927894 with T as the risk allele (het p=0.127). GENR= Generation R.

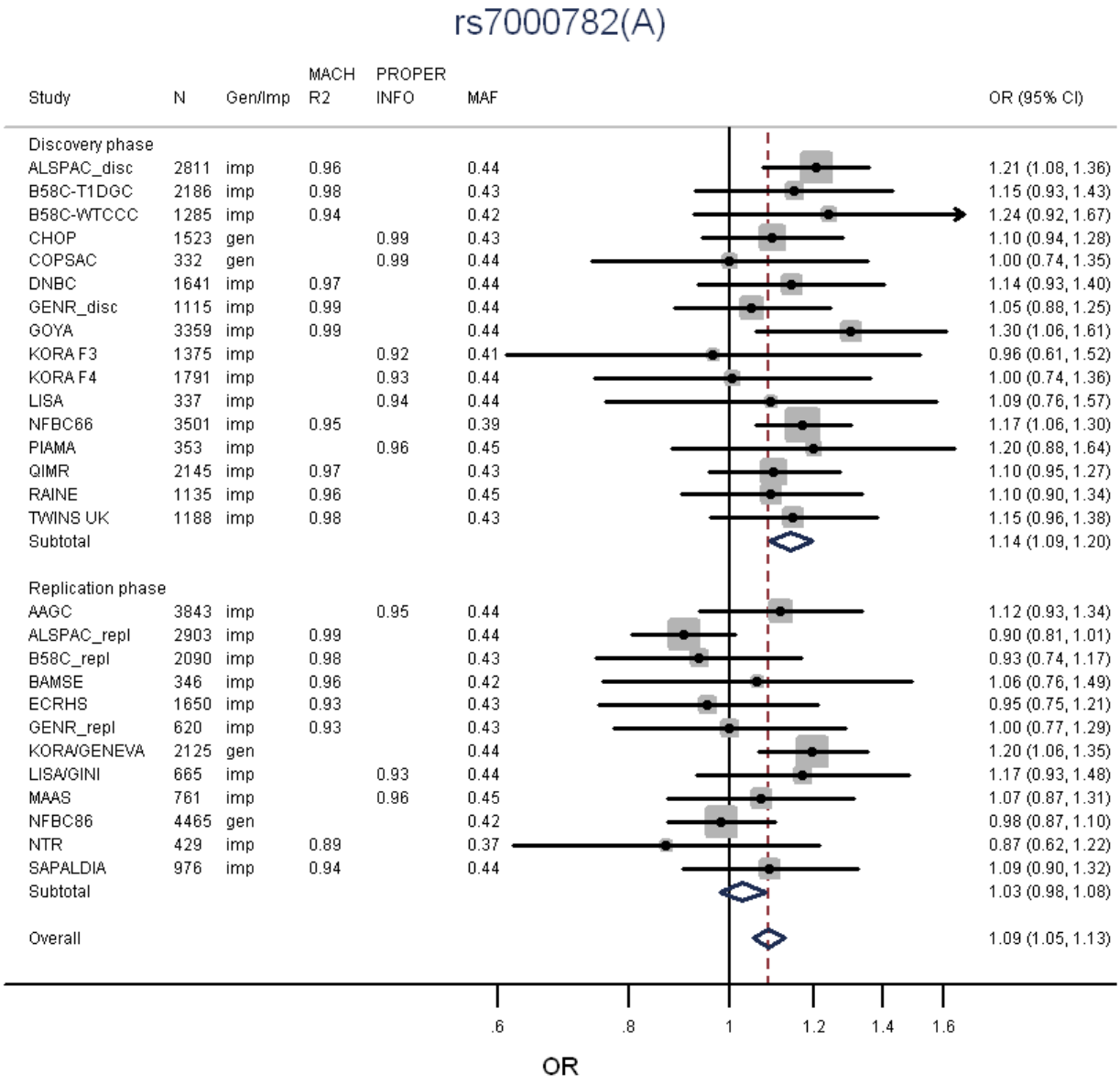
a.

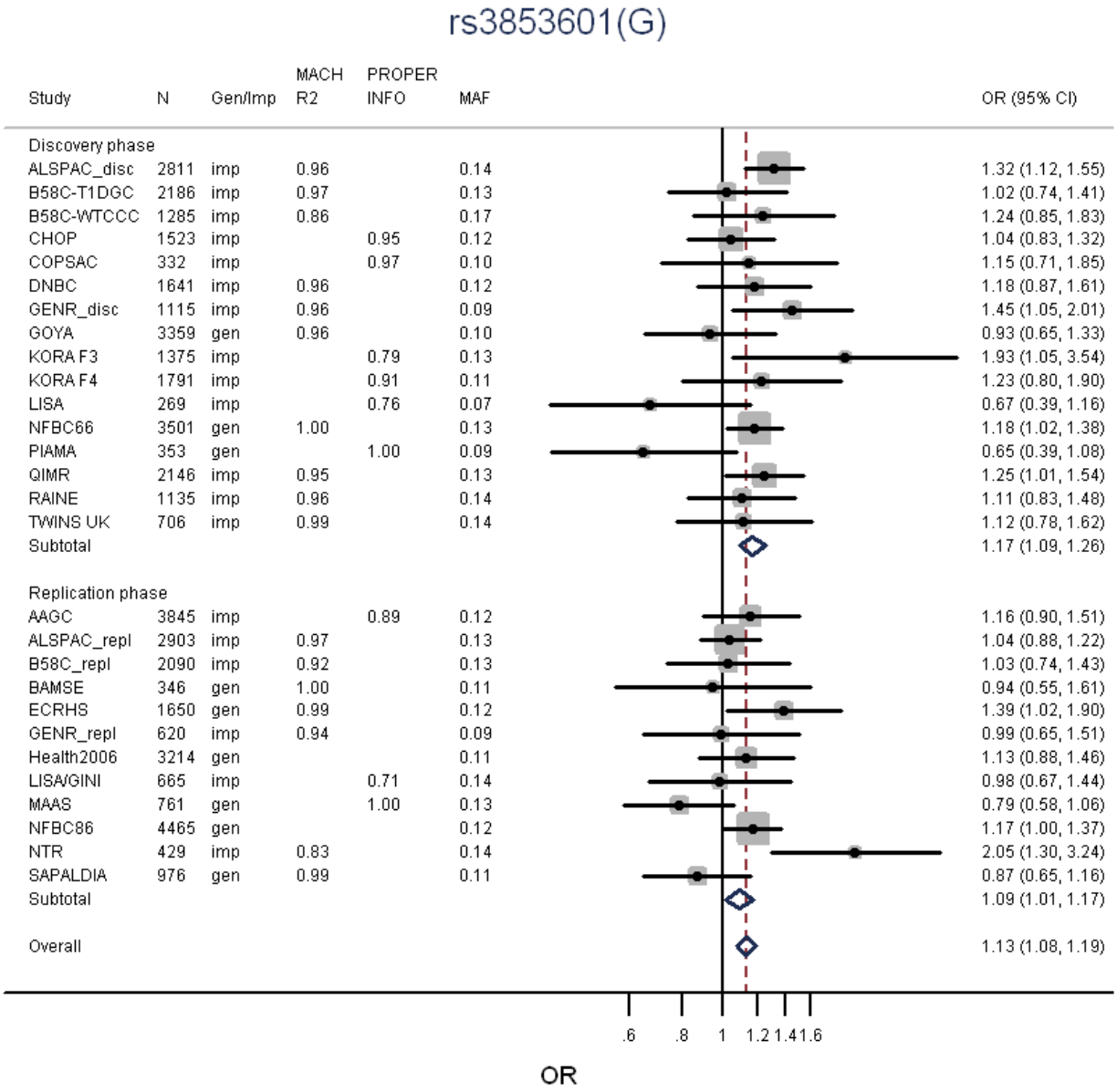


b.

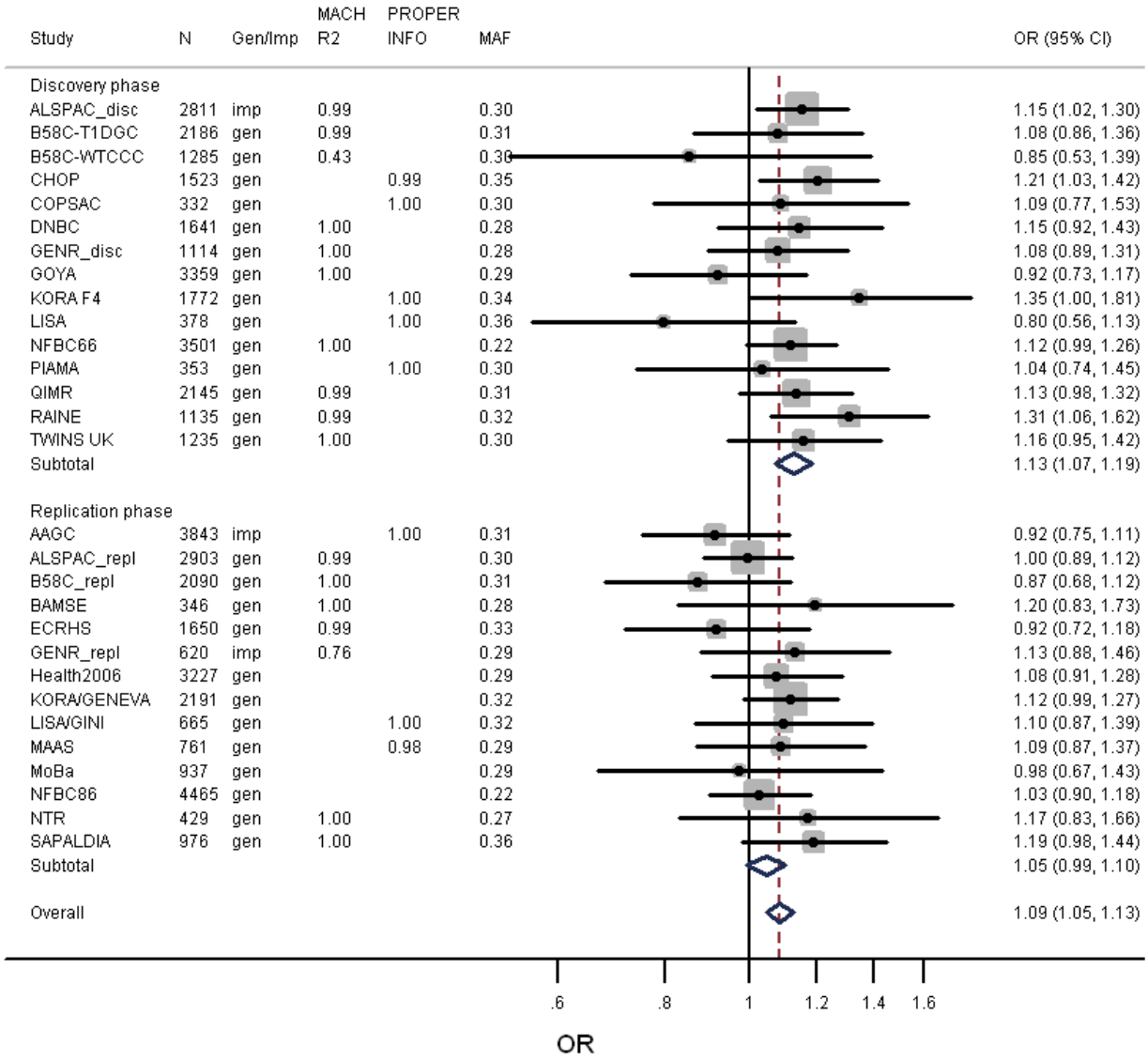


Supplementary Figure 5. Forest plots of the association of the 7 SNPs which did not meet genome-wide significance with atopic dermatitis for the discovery and replication studies.
All ORs are reported with the minor allele (shown in brackets) as the effect allele. *MoBa imputation quality score was 'info' from PLINK. GENR= Generation R. 'gen' in the imputation (Gen/Imp) column refers to SNPs that were on the genome-wide genotyping chip for the discovery samples and were either on the genome-wide genotyping chip or were individually genotyped for the replications samples. Only Health2006, KORA/GENEVA and NFBC86` underwent individual SNP genotyping.

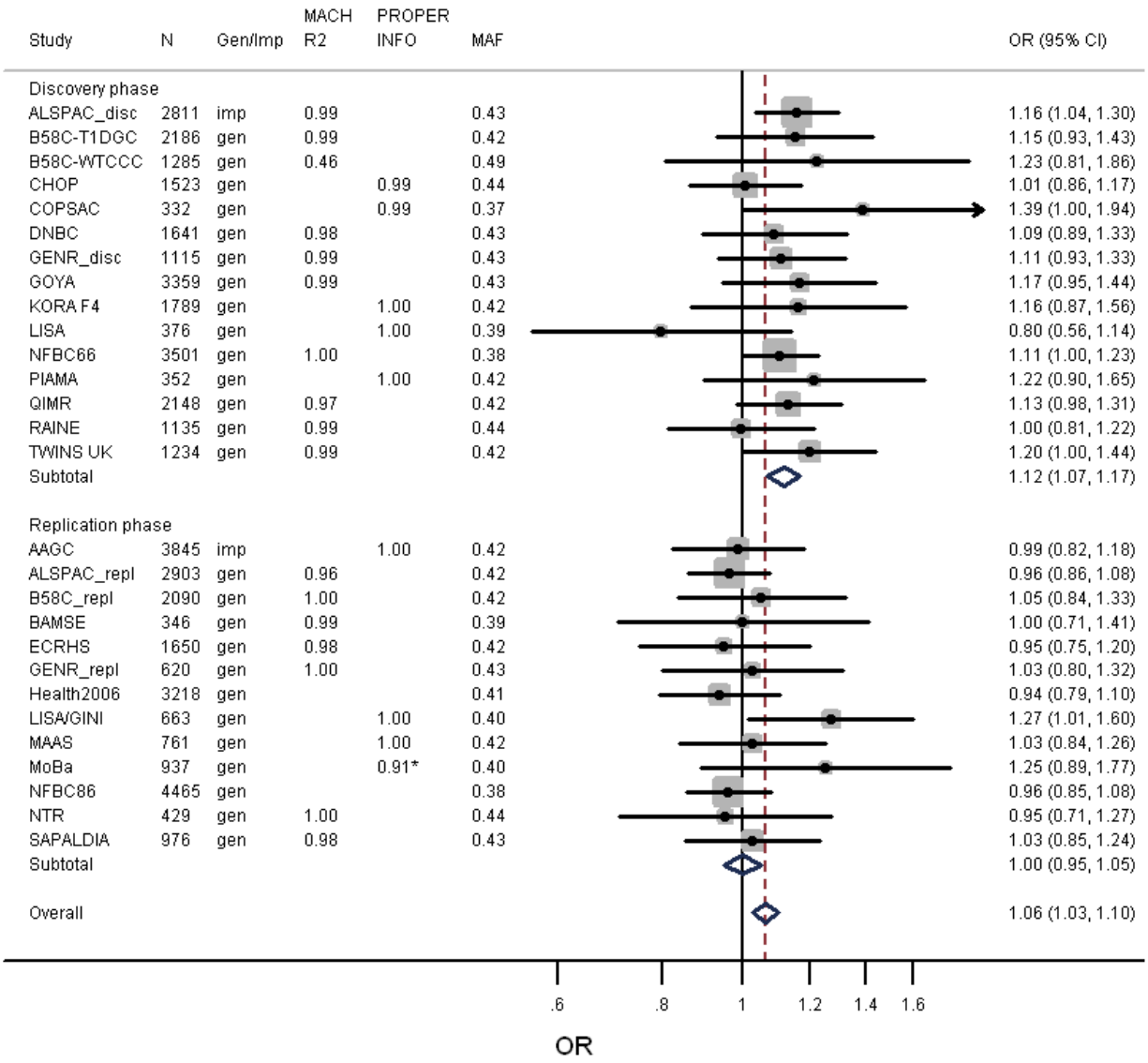


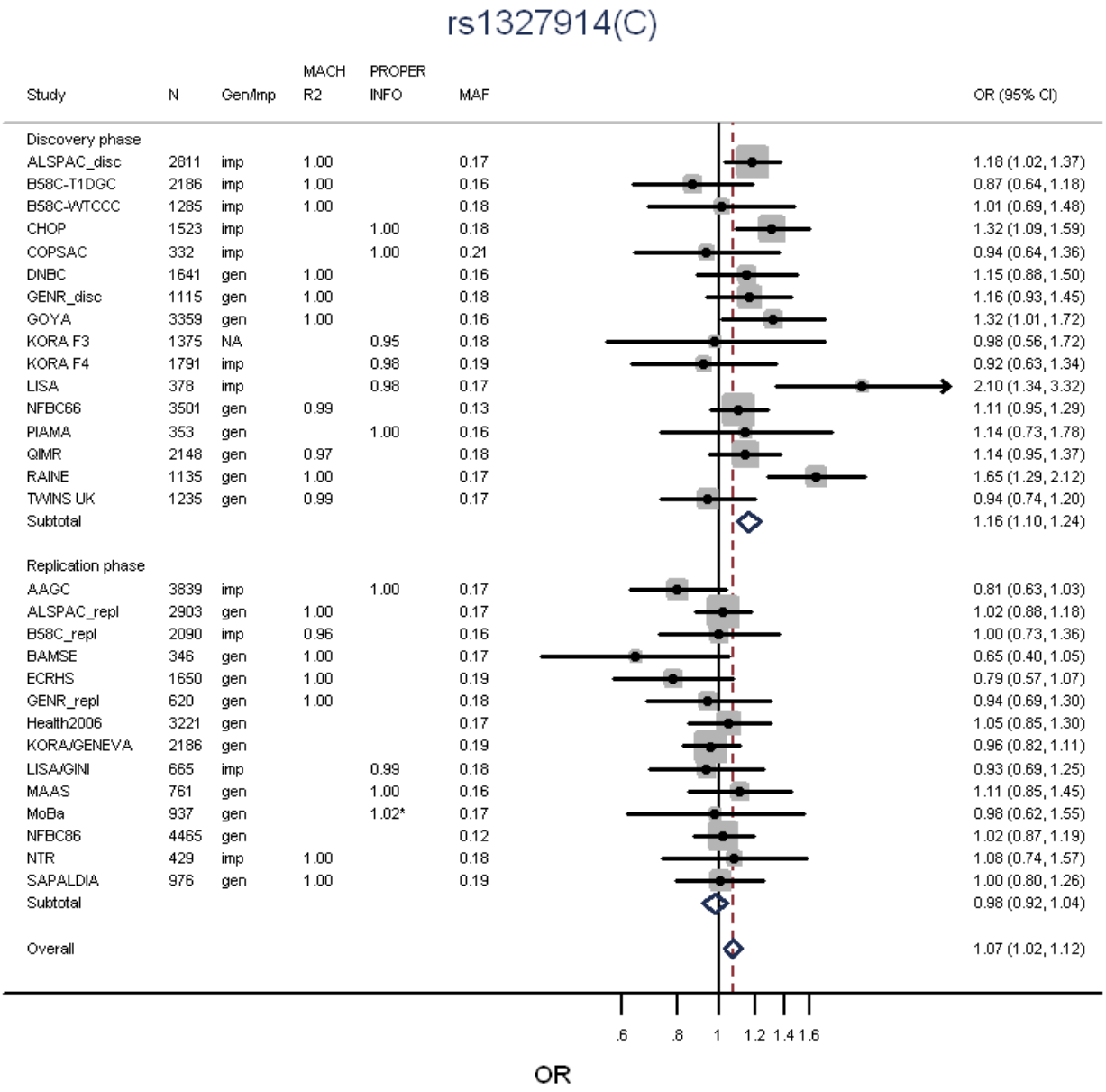

rs3853601(G)
Study
N
Gen/Imp
MACH R2
PROPER INFO
MAF
OR (95% CI)
Discovery phase
ALSPAC_disc 2811 imp 0.96 0.14 1.32 (1.12, 1.55)
B58C-T1DGC 2186 imp 0.97 0.13 1.02 (0.74, 1.41)
B58C-WTCCC 1285 imp 0.86 0.17 1.24 (0.85, 1.83)
CHOP 1523 imp 0.95 0.12 1.04 (0.83, 1.32)
COPSAC 332 imp 0.97 0.10 1.15 (0.71, 1.85)
DNBC 1641 imp 0.96 0.12 1.18 (0.87, 1.61)
GENR_disc 1115 imp 0.96 0.09 1.45 (1.05, 2.01)
GOYA 3359 gen 0.96 0.10 0.93 (0.65, 1.33)
KORA F3 1375 imp 0.79 0.13 1.93 (1.05, 3.54)
KORA F4 1791 imp 0.91 0.11 1.23 (0.80, 1.90)
LISA 269 imp 0.76 0.07 0.67 (0.39, 1.16)
NFBC66 3501 gen 1.00 0.13 1.18 (1.02, 1.38)
PIAMA 353 gen 1.00 0.09 0.65 (0.39, 1.08)
QIMR 2146 imp 0.95 0.13 1.25 (1.01, 1.54)
RAINE 1135 imp 0.96 0.14 1.11 (0.83, 1.48)
TWINS UK 706 imp 0.99 0.14 1.12 (0.78, 1.62)
Subtotal 1.17 (1.09, 1.26)
Replication phase
AAGC 3845 imp 0.89 0.12 1.16 (0.90, 1.51)
ALSPAC_repl 2903 imp 0.97 0.13 1.04 (0.88, 1.22)
B58C_repl 2090 imp 0.92 0.13 1.03 (0.74, 1.43)
BAMSE 346 gen 1.00 0.11 0.94 (0.55, 1.61)
ECRHS 1650 gen 0.99 0.12 1.39 (1.02, 1.90)
GENR_repl 620 imp 0.94 0.09 0.99 (0.65, 1.51)
Health2006 3214 gen 0.11 1.13 (0.88, 1.46)
LISA/GINI 665 imp 0.71 0.14 0.98 (0.67, 1.44)
MAAS 761 gen 1.00 0.13 0.79 (0.58, 1.06)
NFBC86 4465 gen 0.12 1.17 (1.00, 1.37)
NTR 429 imp 0.83 0.14 2.05 (1.30, 3.24)
SAPALDIA 976 gen 0.99 0.11 0.87 (0.65, 1.16)
Subtotal 1.09 (1.01, 1.17)
Overall 1.13 (1.08, 1.19)
.6
.8
1
1.2
1.4
1.6
OR

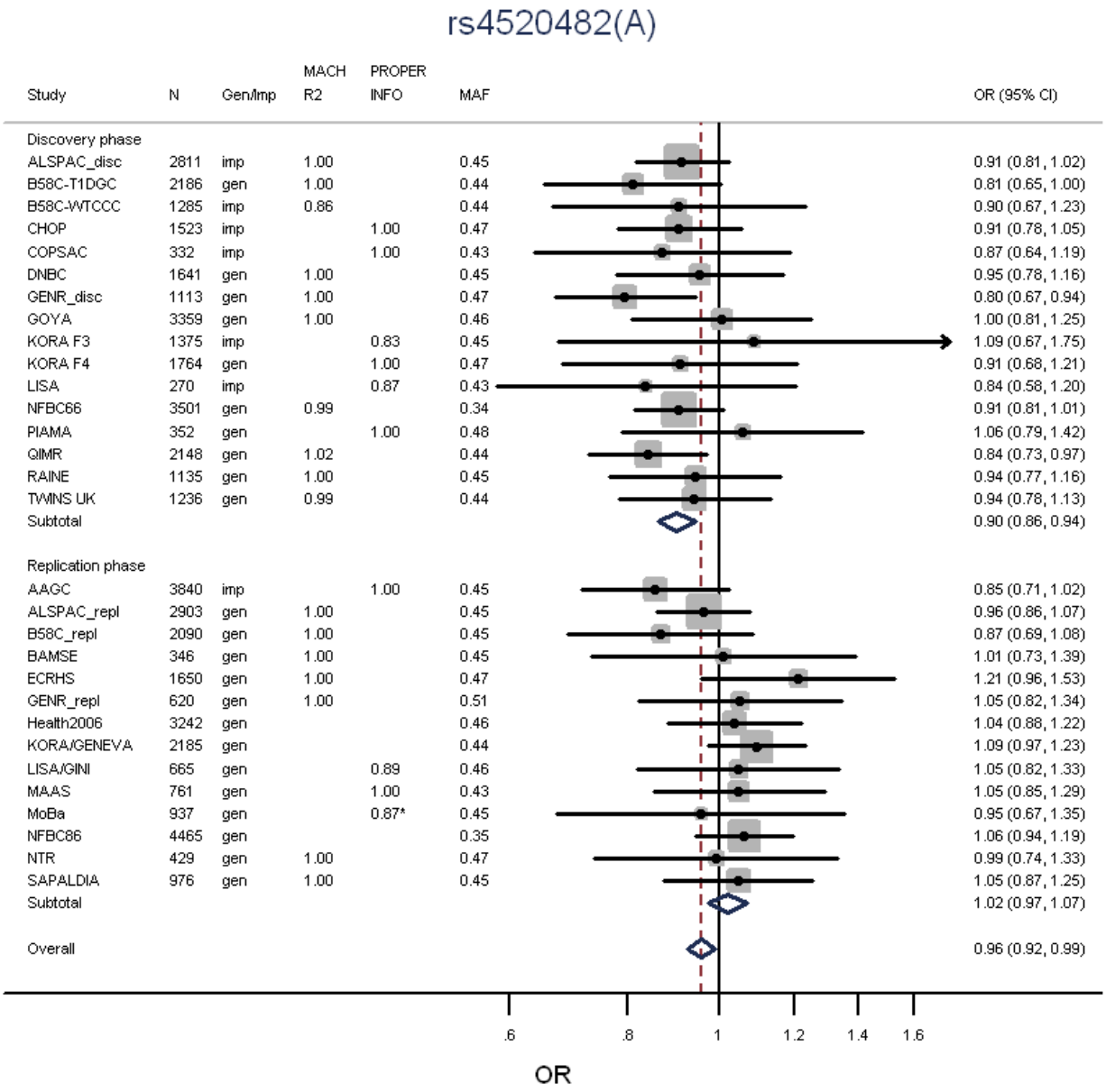
rs4821544(C)

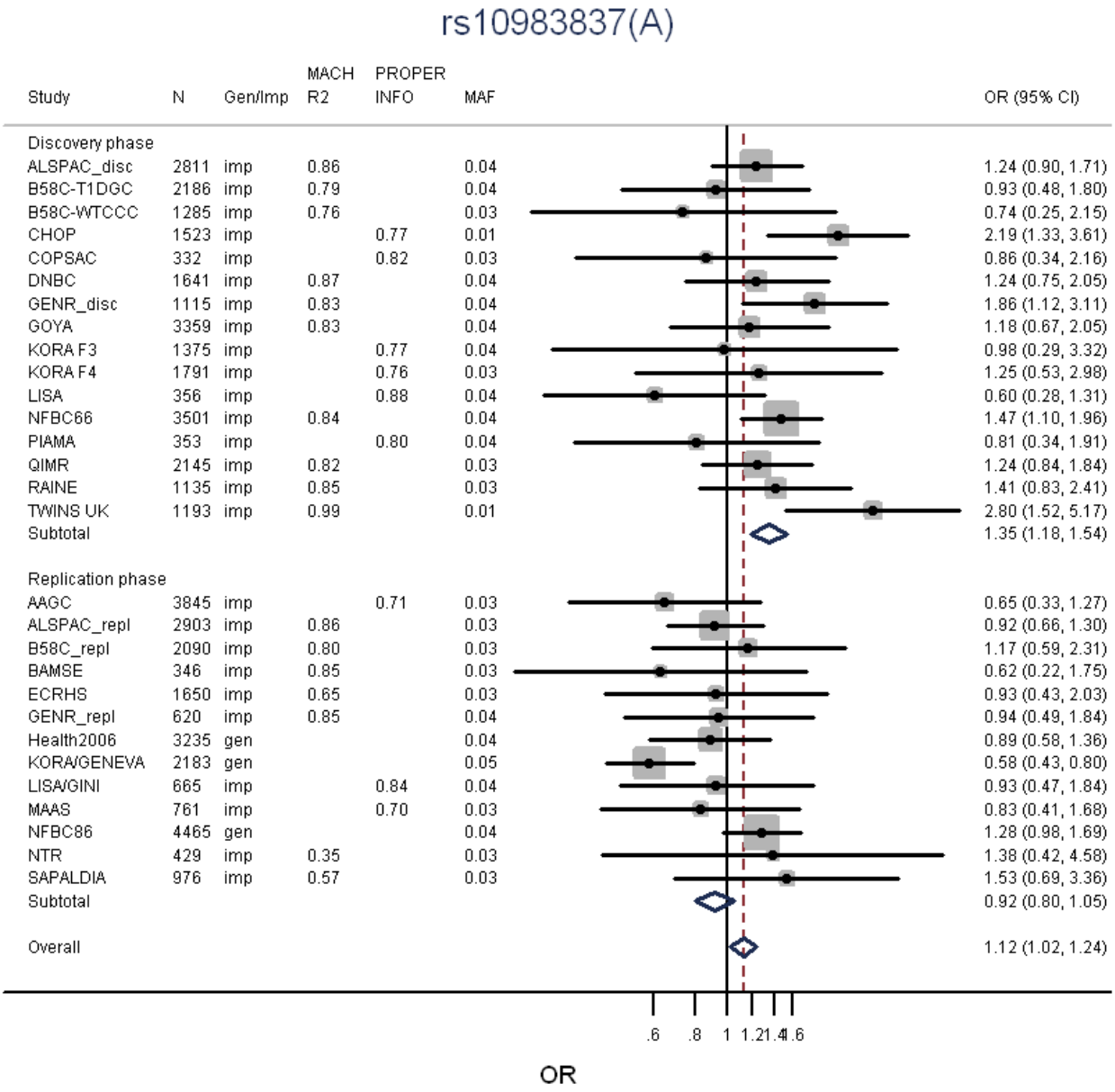

Study
N
Gen/Imp
MACH R2
PROPER INFO
MAF
OR (95% CI)
Discovery phase
ALSPAC_disc 2811 imp 0.99 0.30 1.15 (1.02, 1.30)
B58C-T1DGC 2186 gen 0.99 0.31 1.08 (0.86, 1.36)
B58C-WTCCC 1285 gen 0.43 0.30 0.85 (0.53, 1.39)
CHOP 1523 gen 0.99 0.35 1.21 (1.03, 1.42)
COPSAC 332 gen 1.00 0.30 1.09 (0.77, 1.53)
DNBC 1641 gen 1.00 0.28 1.15 (0.92, 1.43)
GENR_disc 1114 gen 1.00 0.28 1.08 (0.89, 1.31)
GOYA 3359 gen 1.00 0.29 0.92 (0.73, 1.17)
KORA F4 1772 gen 1.00 0.34 1.35 (1.00, 1.81)
LISA 378 gen 1.00 0.36 0.80 (0.56, 1.13)
NFBC66 3501 gen 1.00 0.22 1.12 (0.99, 1.26)
PIAMA 353 gen 1.00 0.30 1.04 (0.74, 1.45)
QIMR 2145 gen 0.99 0.31 1.13 (0.98, 1.32)
RAINE 1135 gen 0.99 0.32 1.31 (1.06, 1.62)
TWINS UK 1235 gen 1.00 0.30 1.16 (0.95, 1.42)
Subtotal 1.13 (1.07, 1.19)
Replication phase
AAGC 3843 imp 1.00 0.31 0.92 (0.75, 1.11)
ALSPAC_repl 2903 gen 0.99 0.30 1.00 (0.89, 1.12)
B58C_repl 2090 gen 1.00 0.31 0.87 (0.68, 1.12)
BAMSE 346 gen 1.00 0.28 1.20 (0.83, 1.73)
ECRHS 1650 gen 0.99 0.33 0.92 (0.72, 1.18)
GENR_repl 620 imp 0.76 0.29 1.13 (0.88, 1.46)
Health2006 3227 gen 0.29 1.08 (0.91, 1.28)
KORA/GENEVA 2191 gen 0.32 1.12 (0.99, 1.27)
LISA/GINI 665 gen 1.00 0.32 1.10 (0.87, 1.39)
MAAS 761 gen 0.98 0.29 1.09 (0.87, 1.37)
MoBa 937 gen 0.29 0.98 (0.67, 1.43)
NFBC86 4465 gen 0.22 1.03 (0.90, 1.18)
NTR 429 gen 1.00 0.27 1.17 (0.83, 1.66)
SAPALDIA 976 gen 1.00 0.36 1.19 (0.98, 1.44)
Subtotal 1.05 (0.99, 1.10)
Overall 1.09 (1.05, 1.13)
.6
.8
1
1.2
1.4
1.6
OR

rs10994675(A)




rs1327914(C)
Study
N
Gen/Imp
MACH R2
PROPER INFO
MAF
OR (95% CI)
Discovery phase
ALSPAC_disc 2811 imp 1.00 0.17 1.18 (1.02, 1.37)
B58C-T1DGC 2186 imp 1.00 0.16 0.87 (0.64, 1.18)
B58C-WTCCC 1285 imp 1.00 0.18 1.01 (0.69, 1.48)
CHOP 1523 imp 1.00 0.18 1.32 (1.09, 1.59)
COPSAC 332 imp 1.00 0.21 0.94 (0.64, 1.36)
DNBC 1641 gen 1.00 0.16 1.15 (0.88, 1.50)
GENR_disc 1115 gen 1.00 0.18 1.16 (0.93, 1.45)
GOYA 3359 gen 1.00 0.16 1.32 (1.01, 1.72)
KORA F3 1375 NA 0.95 0.18 0.98 (0.56, 1.72)
KORA F4 1791 imp 0.98 0.19 0.92 (0.63, 1.34)
LISA 378 imp 0.98 0.17 2.10 (1.34, 3.32)
NFBC66 3501 gen 0.99 0.13 1.11 (0.95, 1.29)
PIAMA 353 gen 1.00 0.16 1.14 (0.73, 1.78)
QIMR 2148 gen 0.97 0.18 1.14 (0.95, 1.37)
RAINE 1135 gen 1.00 0.17 1.65 (1.29, 2.12)
TWINS UK 1235 gen 0.99 0.17 0.94 (0.74, 1.20)
Subtotal 1.16 (1.10, 1.24)
Replication phase
AAGC 3839 imp 1.00 0.17 0.81 (0.63, 1.03)
ALSPAC_repl 2903 gen 1.00 0.17 1.02 (0.88, 1.18)
B58C_repl 2090 imp 0.96 0.16 1.00 (0.73, 1.36)
BAMSE 346 gen 1.00 0.17 0.65 (0.40, 1.05)
ECRHS 1650 gen 1.00 0.19 0.79 (0.57, 1.07)
GENR_repl 620 gen 1.00 0.18 0.94 (0.69, 1.30)
Health2006 3221 gen 0.17 1.05 (0.85, 1.30)
KORA/GENEVA 2186 gen 0.19 0.96 (0.82, 1.11)
LISA/GINI 665 imp 0.99 0.18 0.93 (0.69, 1.25)
MAAS 761 gen 1.00 0.16 1.11 (0.85, 1.45)
MoBa 937 gen 1.02* 0.17 0.98 (0.62, 1.55)
NFBC86 4465 gen 0.12 1.02 (0.87, 1.19)
NTR 429 imp 1.00 0.18 1.08 (0.74, 1.57)
SAPALDIA 976 gen 1.00 0.19 1.00 (0.80, 1.26)
Subtotal 0.98 (0.92, 1.04)
Overall 1.07 (1.02, 1.12)
.6
.8
1
1.2
1.4
1.6
OR

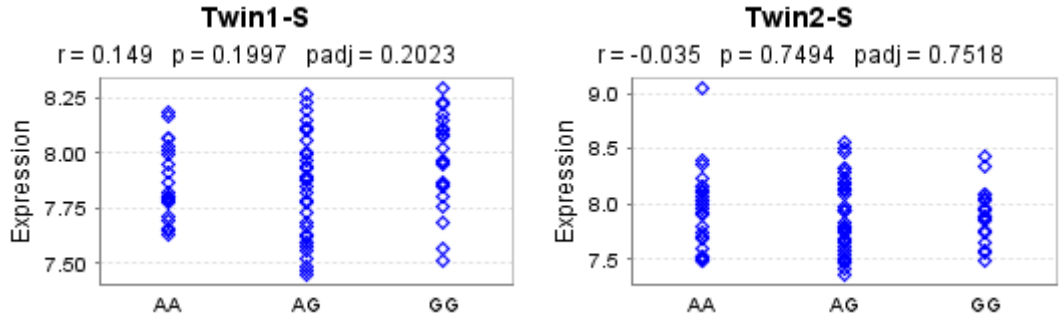

rs4520482(A)
Study
N
Gen/Imp
MACH R2
PROPER INFO
MAF
OR (95% CI)
Discovery phase
ALSPAC_disc 2811 imp 1.00 0.45 0.91 (0.81, 1.02)
B58C-T1DGC 2186 gen 1.00 0.44 0.81 (0.65, 1.00)
B58C-WTCCC 1285 imp 0.86 0.44 0.90 (0.67, 1.23)
CHOP 1523 imp 1.00 0.47 0.91 (0.78, 1.05)
COPSAC 332 imp 1.00 0.43 0.87 (0.64, 1.19)
DNBC 1641 gen 1.00 0.45 0.95 (0.78, 1.16)
GENR_disc 1113 gen 1.00 0.47 0.80 (0.67, 0.94)
GOYA 3359 gen 1.00 0.46 1.00 (0.81, 1.25)
KORA F3 1375 imp 0.83 0.45 1.09 (0.67, 1.75)
KORA F4 1764 gen 1.00 0.47 0.91 (0.68, 1.21)
LISA 270 imp 0.87 0.43 0.84 (0.58, 1.20)
NFBC66 3501 gen 0.99 0.34 0.91 (0.81, 1.01)
PIAMA 352 gen 1.00 0.48 1.06 (0.79, 1.42)
QIMR 2148 gen 1.02 0.44 0.84 (0.73, 0.97)
RAINE 1135 gen 1.00 0.45 0.94 (0.77, 1.16)
TWINS UK 1236 gen 0.99 0.44 0.94 (0.78, 1.13)
Subtotal 0.90 (0.86, 0.94)
Replication phase
AAGC 3840 imp 1.00 0.45 0.85 (0.71, 1.02)
ALSPAC_repl 2903 gen 1.00 0.45 0.96 (0.86, 1.07)
B58C_repl 2090 gen 1.00 0.45 0.87 (0.69, 1.08)
BAMSE 346 gen 1.00 0.45 1.01 (0.73, 1.39)
ECRHS 1650 gen 1.00 0.47 1.21 (0.96, 1.53)
GENR_repl 620 gen 1.00 0.51 1.05 (0.82, 1.34)
Health2006 3242 gen 0.46 1.04 (0.88, 1.22)
KORA/GENEVA 2185 gen 0.44 1.09 (0.97, 1.23)
LISA/GINI 665 gen 0.89 0.46 1.05 (0.82, 1.33)
MAAS 761 gen 1.00 0.43 1.05 (0.85, 1.29)
MoBa 937 gen 0.87* 0.45 0.95 (0.67, 1.35)
NFBC86 4465 gen 0.35 1.06 (0.94, 1.19)
NTR 429 gen 1.00 0.47 0.99 (0.74, 1.33)
SAPALDIA 976 gen 1.00 0.45 1.05 (0.87, 1.25)
Subtotal 1.02 (0.97, 1.07)
Overall 0.96 (0.92, 0.99)
.6
.8
1
1.2
1.4
1.6
OR


rs10983837(A)
Study
N
Gen/Imp
MACH R2
PROPER INFO
MAF
OR (95% CI)
Discovery phase
ALSPAC_disc 2811 imp 0.86 0.04 1.24 (0.90, 1.71)
B58C-T1DGC 2186 imp 0.79 0.04 0.93 (0.48, 1.80)
B58C-WTCCC 1285 imp 0.76 0.03 0.74 (0.25, 2.15)
CHOP 1523 imp 0.77 0.01 2.19 (1.33, 3.61)
COPSAC 332 imp 0.82 0.03 0.86 (0.34, 2.16)
DNBC 1641 imp 0.87 0.04 1.24 (0.75, 2.05)
GENR_disc 1115 imp 0.83 0.04 1.86 (1.12, 3.11)
GOYA 3359 imp 0.83 0.04 1.18 (0.67, 2.05)
KORA F3 1375 imp 0.77 0.04 0.98 (0.29, 3.32)
KORA F4 1791 imp 0.76 0.03 1.25 (0.53, 2.98)
LISA 356 imp 0.88 0.04 0.60 (0.28, 1.31)
NFBC66 3501 imp 0.84 0.04 1.47 (1.10, 1.96)
PIAMA 353 imp 0.80 0.04 0.81 (0.34, 1.91)
QIMR 2145 imp 0.82 0.03 1.24 (0.84, 1.84)
RAINE 1135 imp 0.85 0.03 1.41 (0.83, 2.41)
TWINS UK 1193 imp 0.99 0.01 2.80 (1.52, 5.17)
Subtotal 1.35 (1.18, 1.54)
Replication phase
AAGC 3845 imp 0.71 0.03 0.65 (0.33, 1.27)
ALSPAC_repl 2903 imp 0.86 0.03 0.92 (0.66, 1.30)
B58C_repl 2090 imp 0.80 0.03 1.17 (0.59, 2.31)
BAMSE 346 imp 0.85 0.03 0.62 (0.22, 1.75)
ECRHS 1650 imp 0.65 0.03 0.93 (0.43, 2.03)
GENR_repl 620 imp 0.85 0.04 0.94 (0.49, 1.84)
Health2006 3235 gen 0.04 0.89 (0.58, 1.36)
KORA/GENEVA 2183 gen 0.05 0.58 (0.43, 0.80)
LISA/GINI 665 imp 0.84 0.04 0.93 (0.47, 1.84)
MAAS 761 imp 0.70 0.03 0.83 (0.41, 1.68)
NFBC86 4465 gen 0.04 1.28 (0.98, 1.69)
NTR 429 imp 0.35 0.03 1.38 (0.42, 4.58)
SAPALDIA 976 imp 0.57 0.03 1.53 (0.69, 3.36)
Subtotal 0.92 (0.80, 1.05)
Overall 1.12 (1.02, 1.24)
.6
.8
1
1.2
1.4
1.6
OR

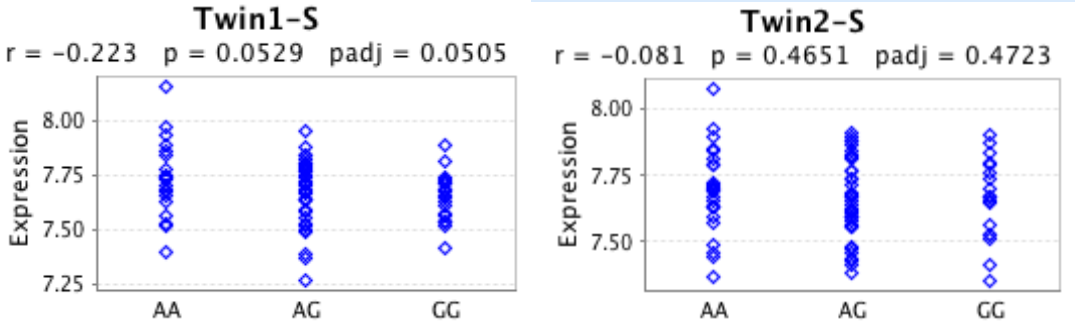
Supplementary Figure 6. MuTHER pilot eQTL skin data for probes within 1Mb of the SNP (a) rs479844, (b) rs2164983 and (c) rs2897442 for 160 female twins. Data is split into two sets (with one of each twin pair in each). Results are shown for the candidate genes near to the SNP of interest (*OVOL1/*, *ACTL9/ADAMTS10*, *KIF3A/IL4/IL13*) and for any gene with p<0.01 (within 1Mb of the SNP) in either twin set. r=regression coefficient, p= unadjusted p-value, padj=adjusted p-value, 10,000 permutations.

a. rs479884

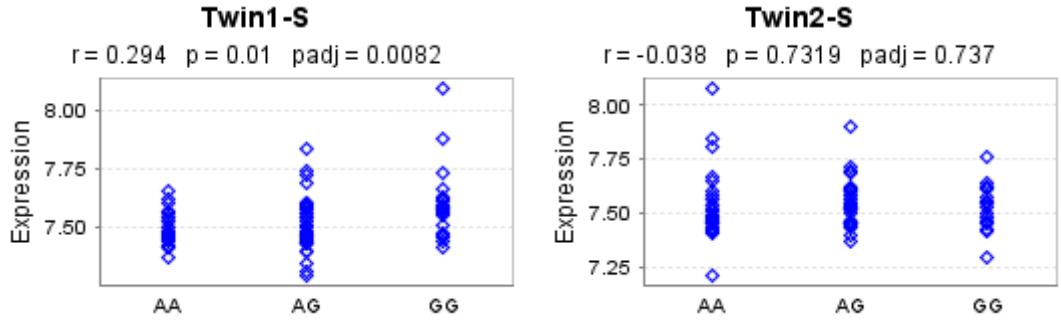
i. *OVOL1* – closest gene. Probe=ILMN_1692936



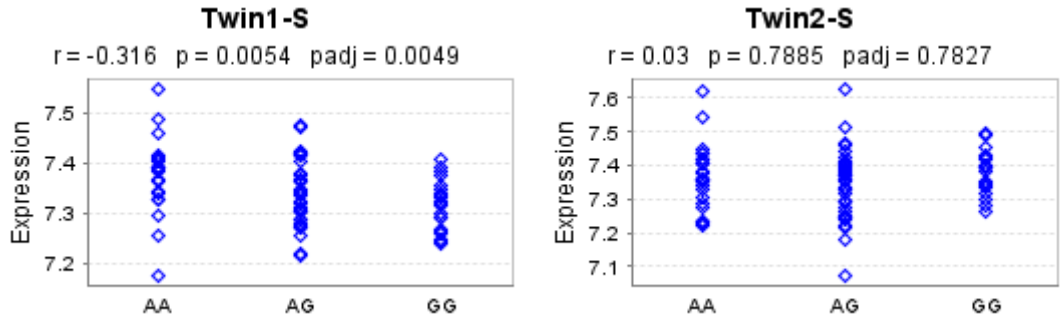
ii. DKFZp761E198 - close gene. Probe=ILMN_1717594



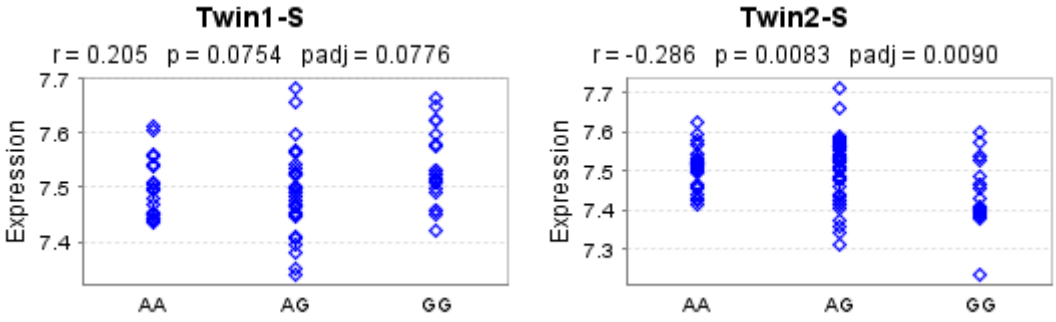
iii *KLC2* – p<0.01 in Twin1. Not confirmed in Twin2. Probe=ILMN_1653470



iv. *LTBP3* – p<0.01 in Twin1. Not confirmed in Twin2. Probe=ILMN_1777121

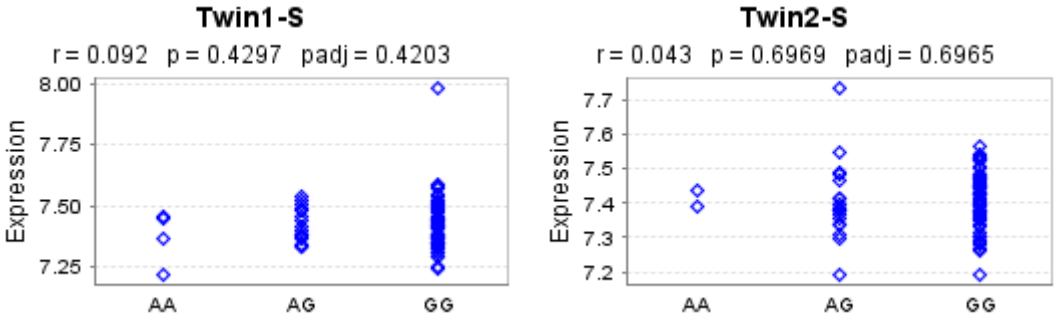


v. *SLC25A45* – p<0.01 in Twin2. Not confirmed in Twin1. Probe=ILMN_1810727



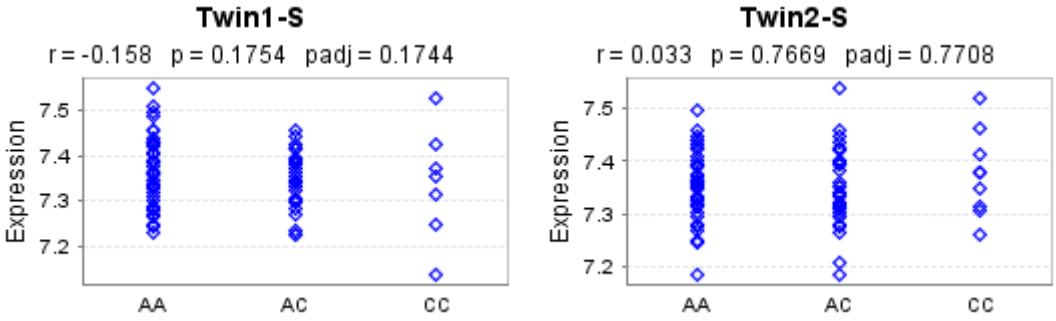
b. rs2967675 – best available proxy for rs2164983 (r^2=0.94)

i. *ACTL9* – closest gene. Probe=ILMN_1656193

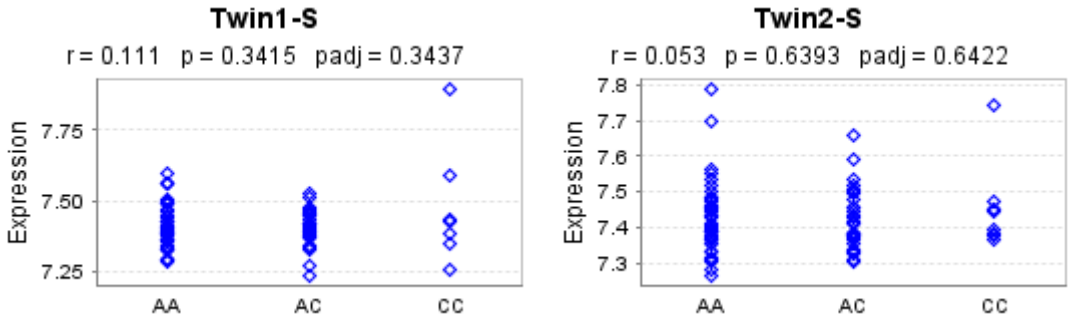


c. rs2299009 – best available proxy for rs2897442 (r^2=1.0)

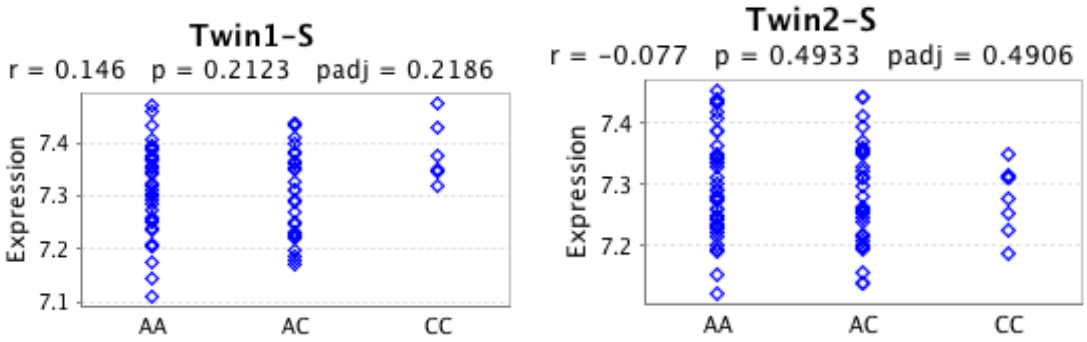
i. *KIF3A* – close gene. Probe=ILMN_1653385



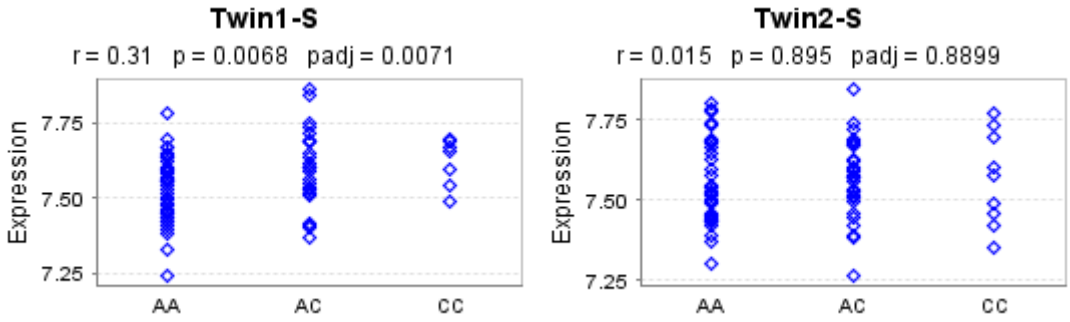
iii.*IL4* -close gene. Probe=ILMN_1669174



iv. IL13 – close gene. Probe=ILMN_2052511

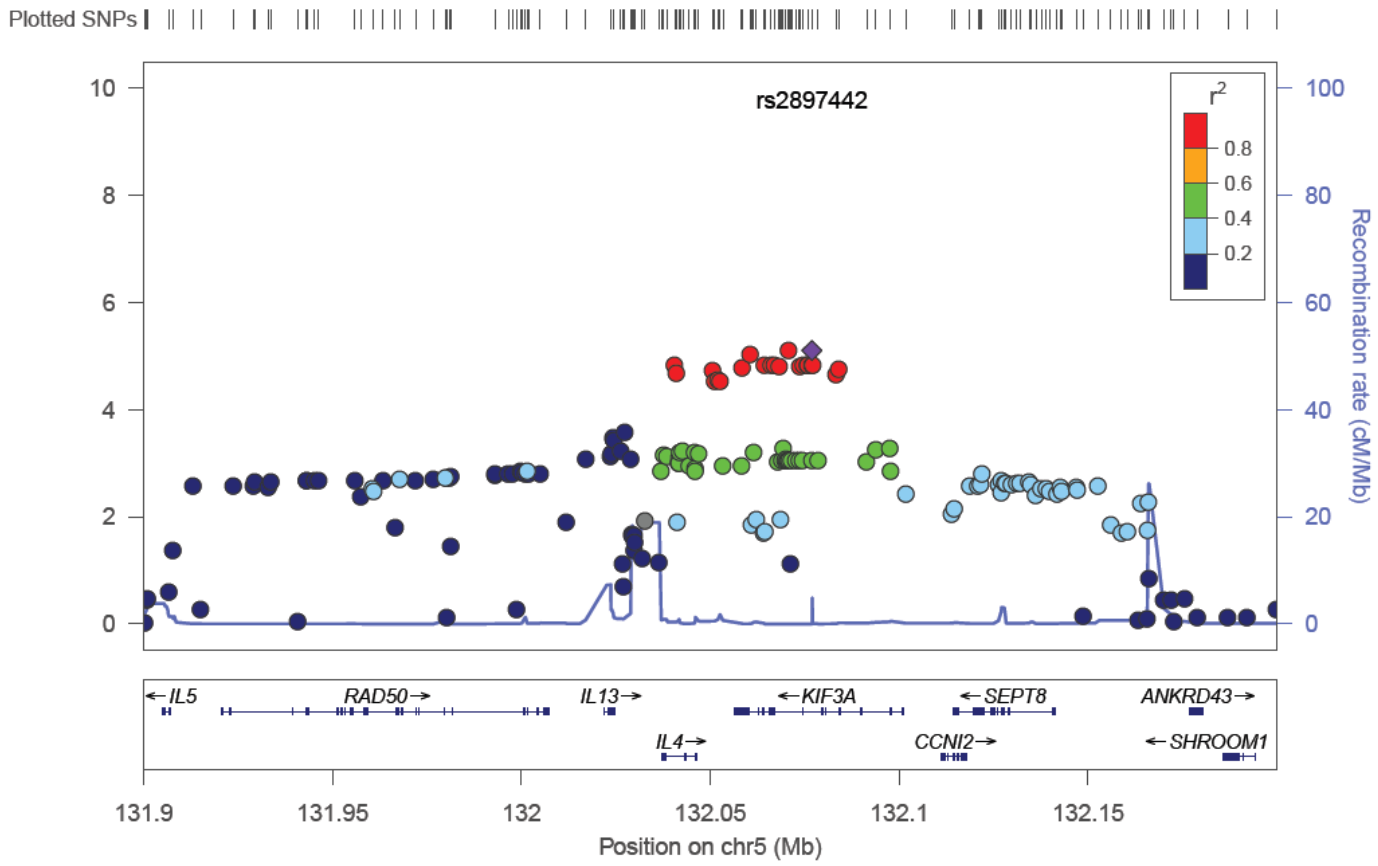


iv. *HSPA4* – p<0.01 in Twin1. Not confirmed in Twin2. Probe=ILMN_175513

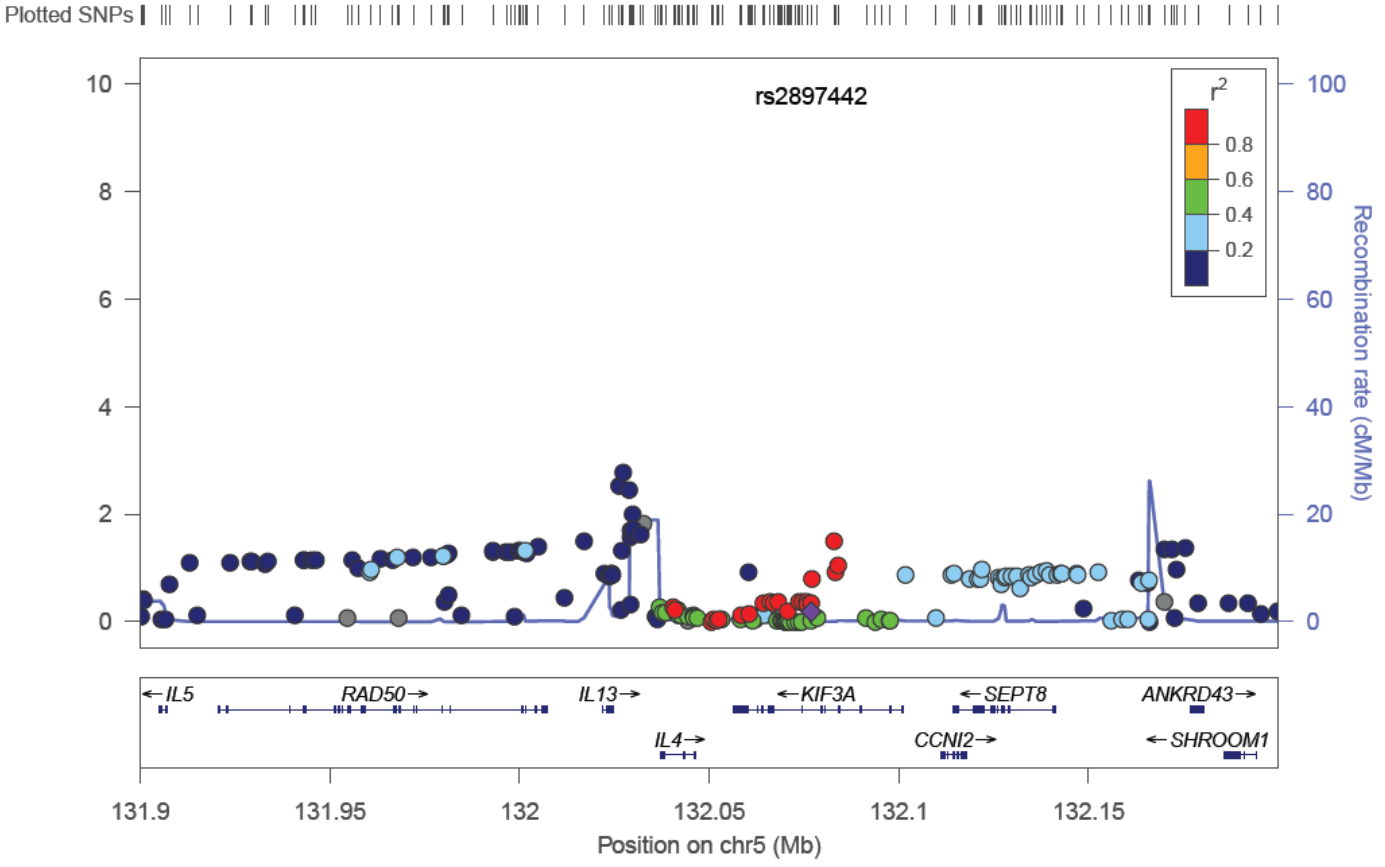


Supplementary Figure 7. Regional Association Plots for 5q31.1 in the discovery cohorts (a) no conditional SNPs and (b) conditional on rs2897442. N=26,164.

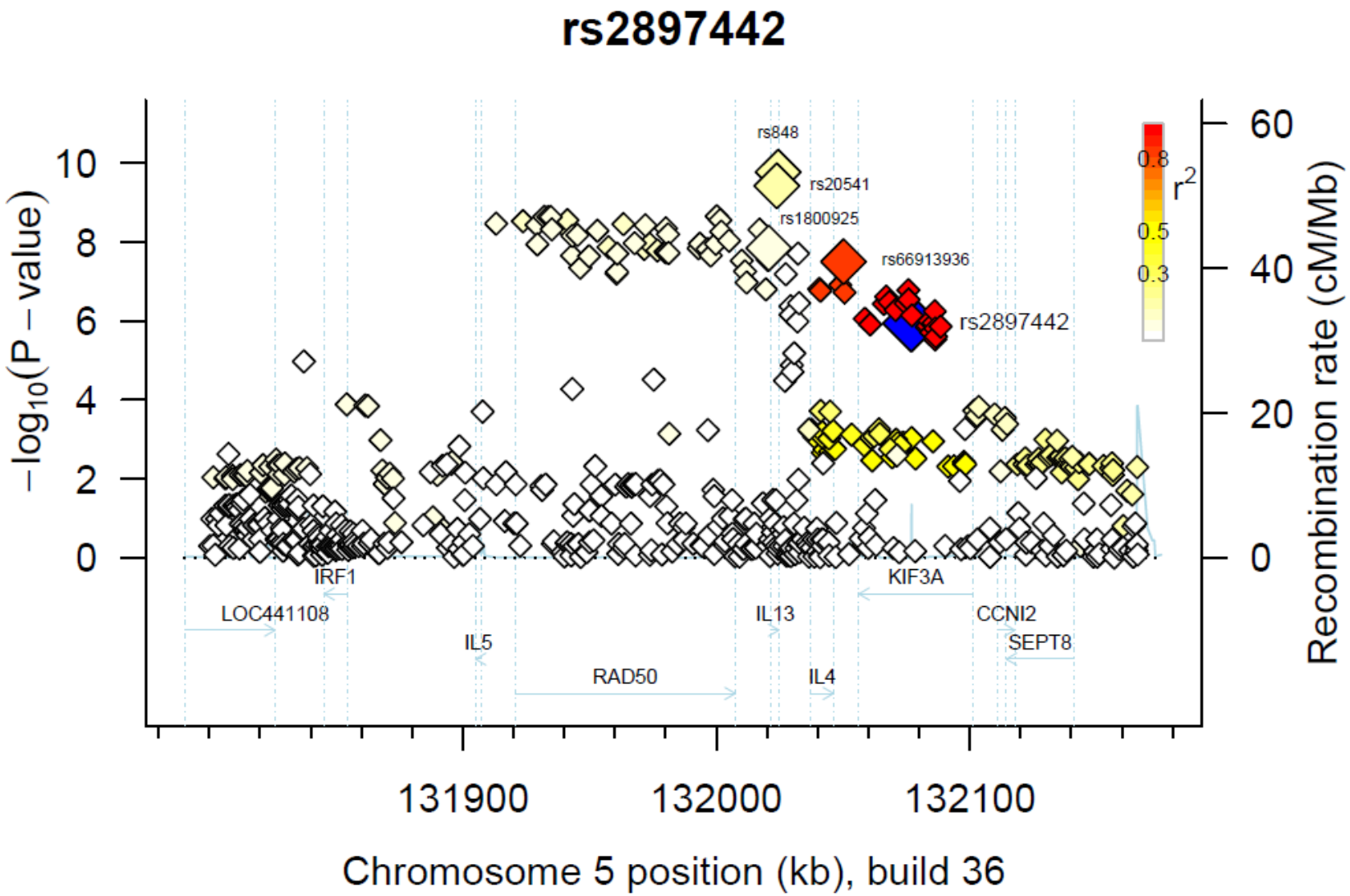
a.



b.

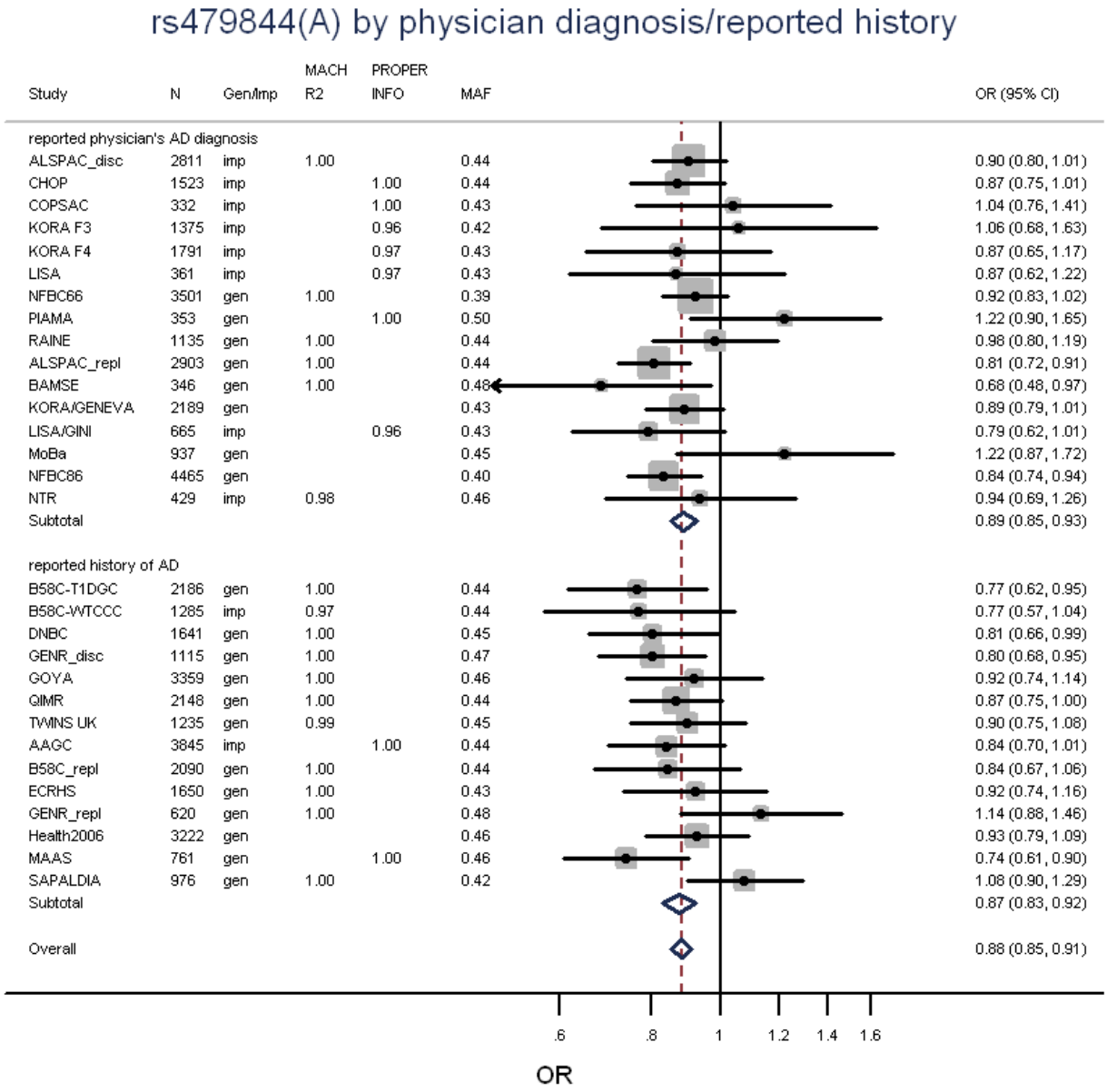


Supplementary Figure 8. Regional association plot of markers within the cytokine cluster on 5q31.1. Results from the Immunochip (custom genotyping SNP- chip designed for immunogenetic studies) including *IL13* polymorphisms previously shown to be associated with asthma and psoriasis risk, as well as the GWAS *KIF3A* polymorphism showing the strongest association in the meta-analysis and the lead SNP of the corresponding putative LD-block from the finemapping approach.

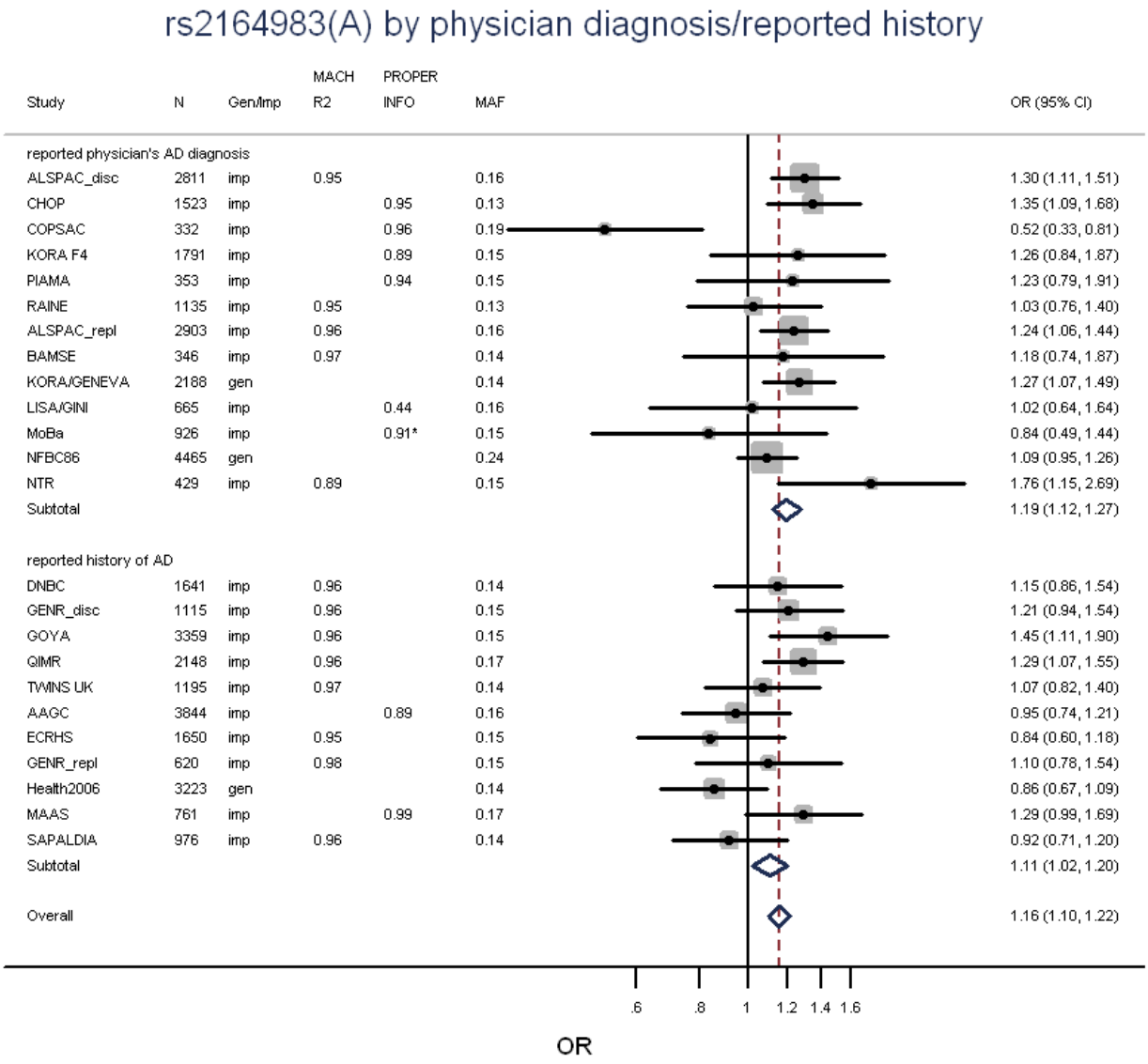


Supplementary Figure 9. Stratified forest plots for SNPs associated with AD (rs479844, rs2164983, rs2897442) or with evidence of heterogeneity (rs2164983, rs1327914, rs10983837). Stratified by (a) reported physician AD diagnosis versus reported history of AD, (b) diagnosis before the age of 15 (child) versus up to and including adults. GENR = Generation R.

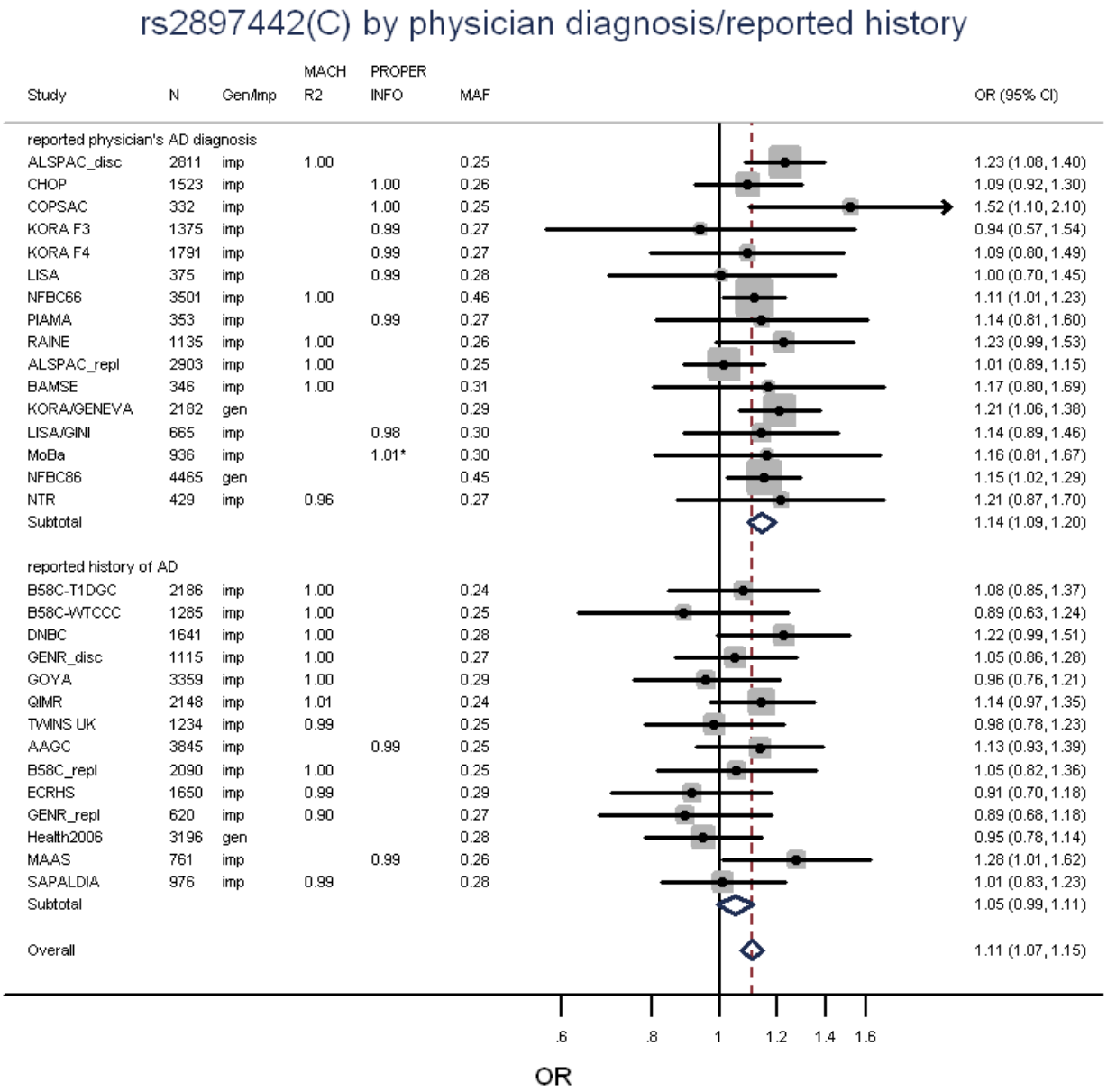
a. **reported physician AD diagnosis versus reported history of AD.** Difference between subgroup p-values: rs479844 p=0.653; rs2164983 p=0.134; rs2897442 p=0.023; rs1327914 p=0.191; rs10983837 p=0.568.



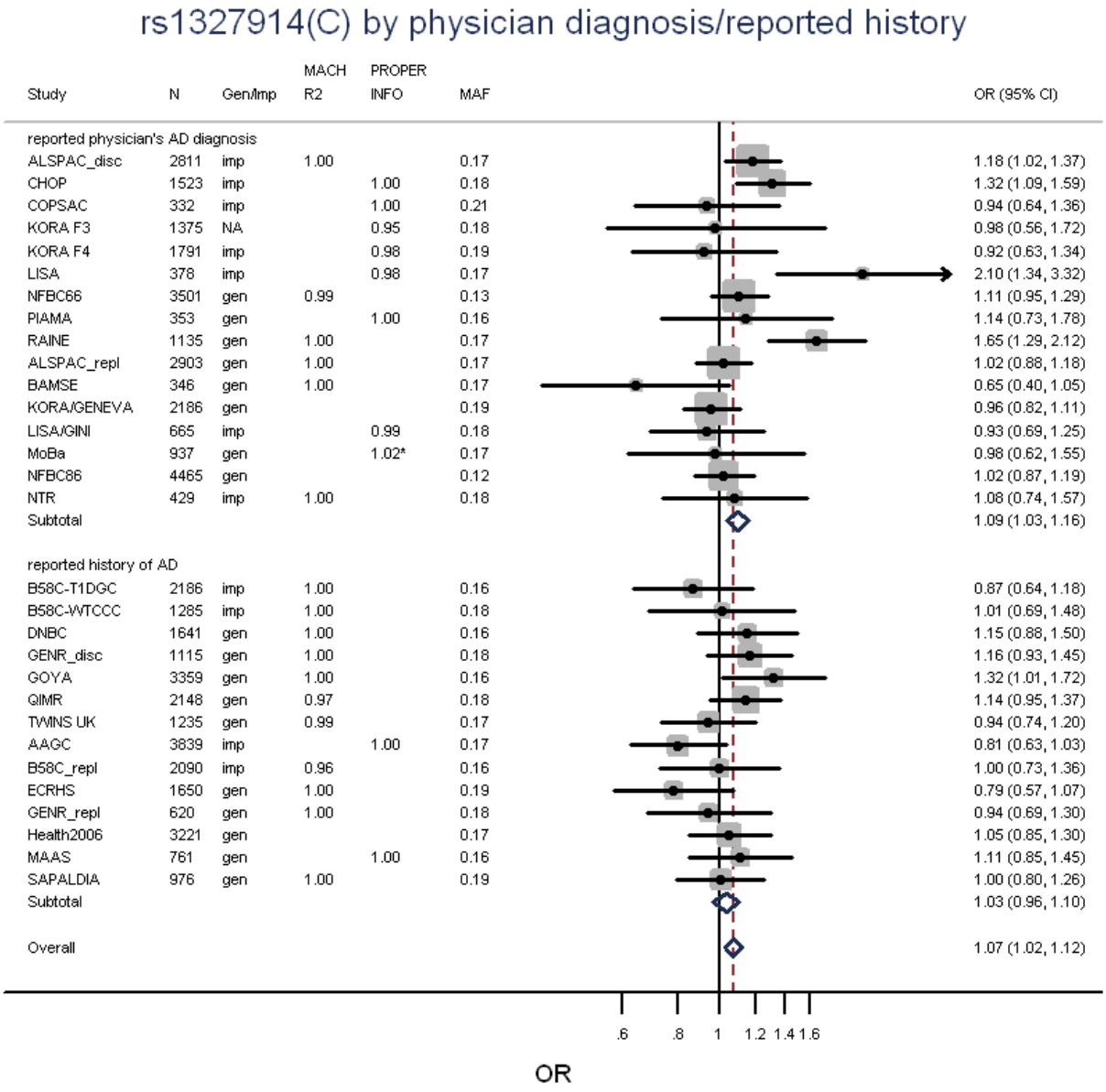
*CHOP used sub-optimal ICD9 diagnosis in medical record to identify cases. Reported physician's AD diagnosis subgroup result with CHOP excluded: OR=0.89 (95%CI 0.85 - 0.93).



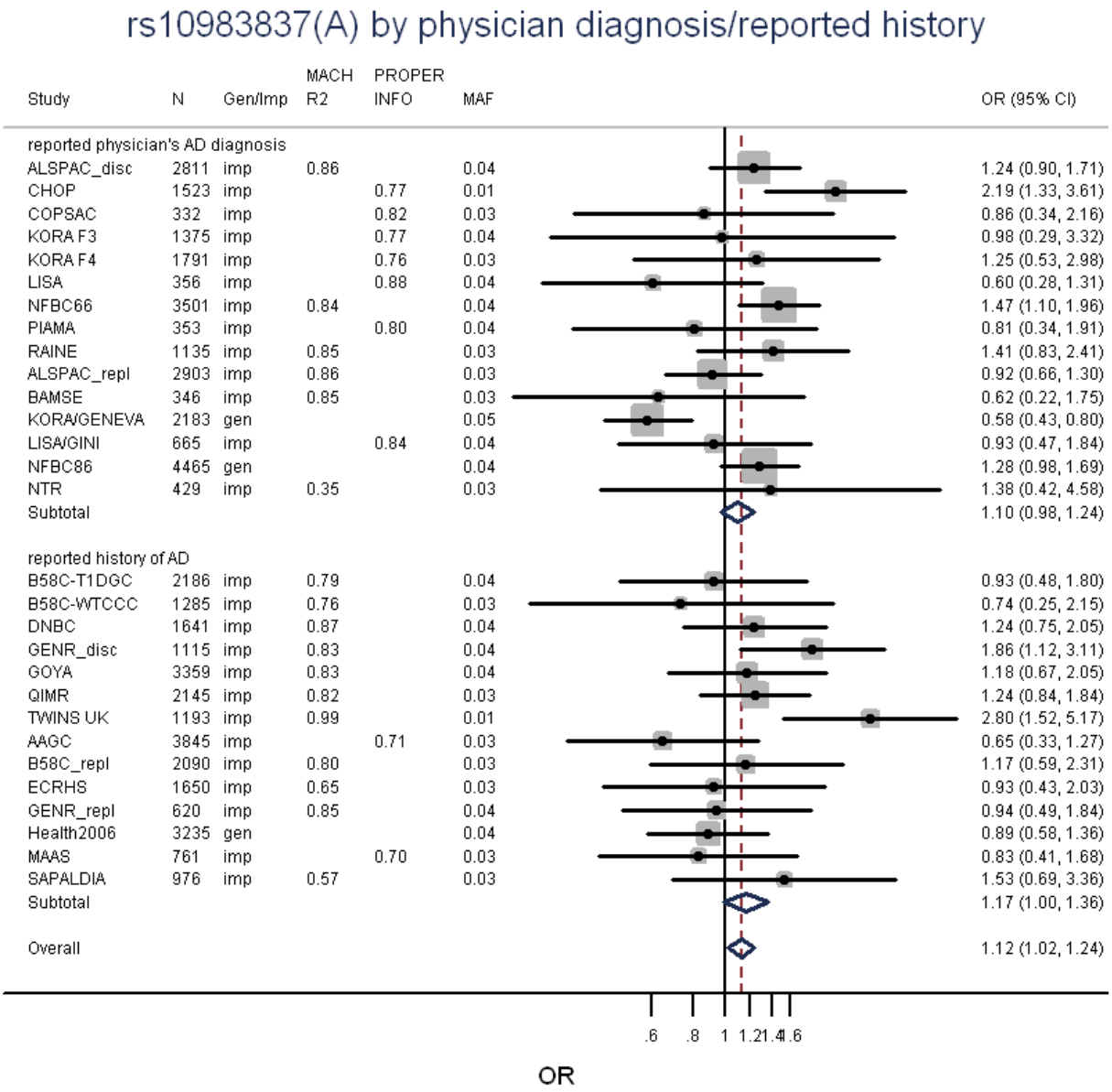
*CHOP used sub-optimal ICD9 diagnosis in medical record to identify cases. Reported physician's AD diagnosis subgroup result with CHOP excluded: OR=1.18 (95%CI 1.10 - 1.26).



*CHOP used sub-optimal ICD9 diagnosis in medical record to identify cases. Reported physician's AD diagnosis subgroup result with CHOP excluded: OR=1.15 (95%CI 1.09 - 1.20).

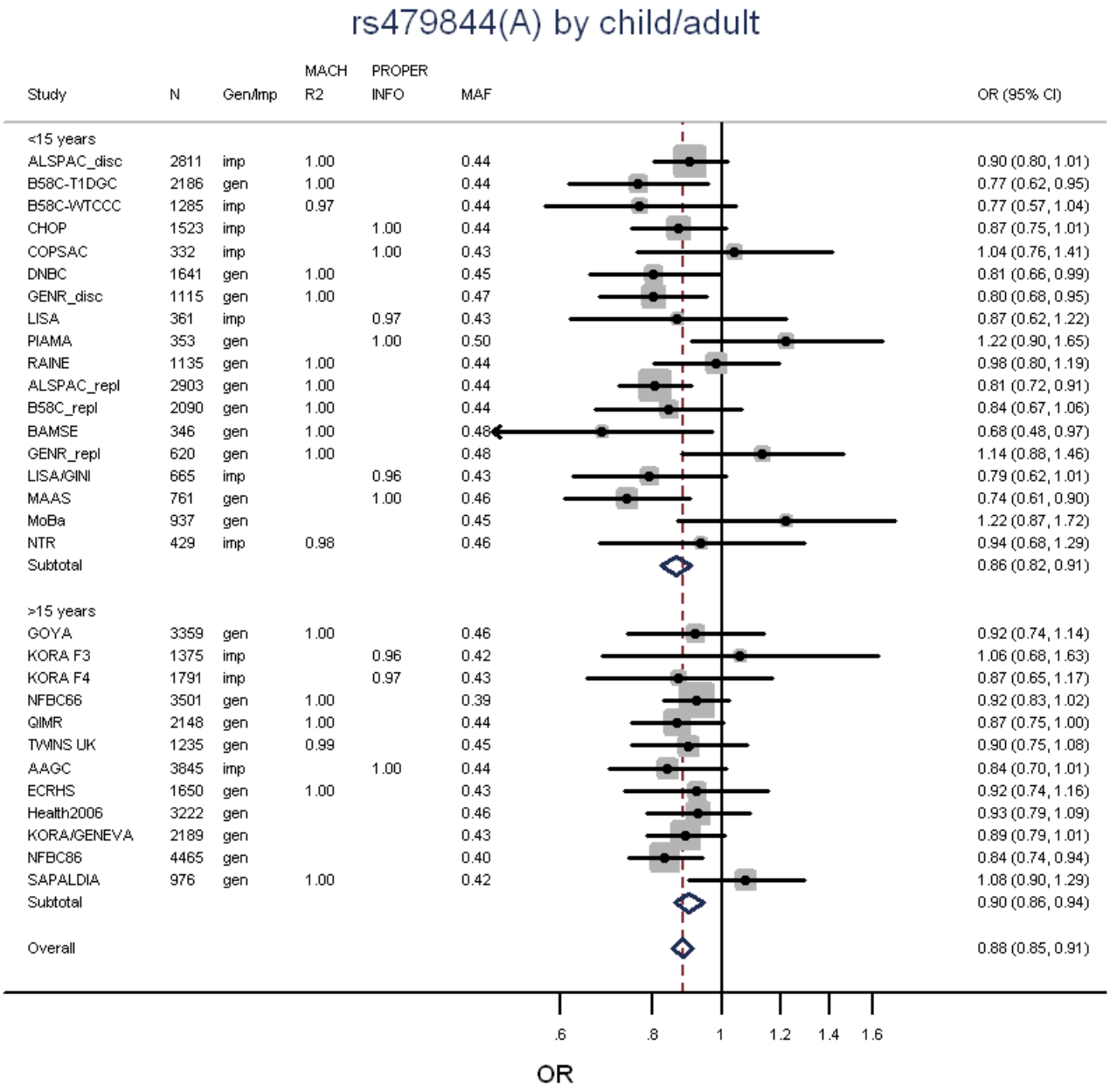


*CHOP used sub-optimal ICD9 diagnosis in medical record to identify cases. Reported physician's AD diagnosis subgroup result with CHOP excluded: OR=1.07 (95%CI 1.01 - 1.14).

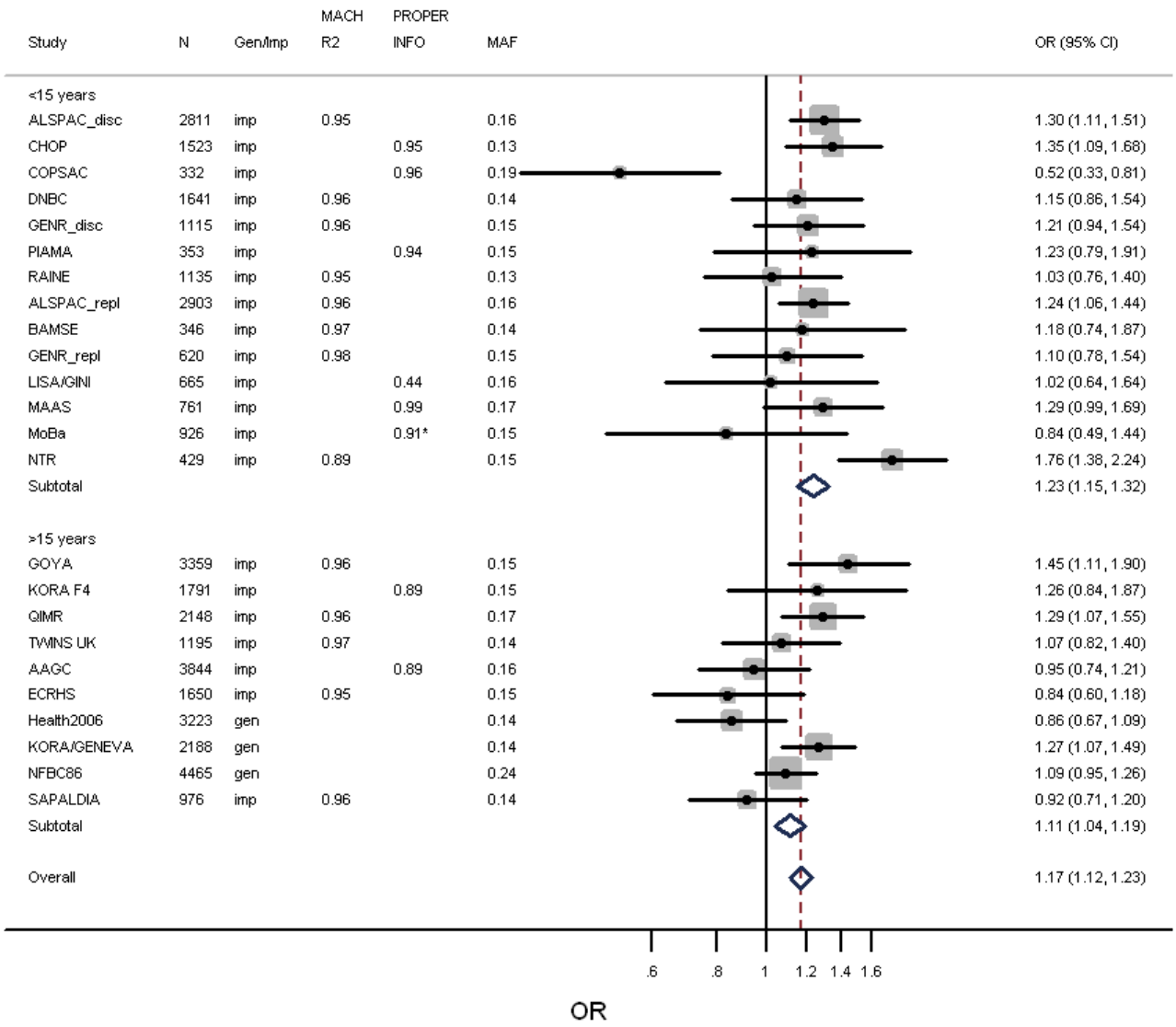


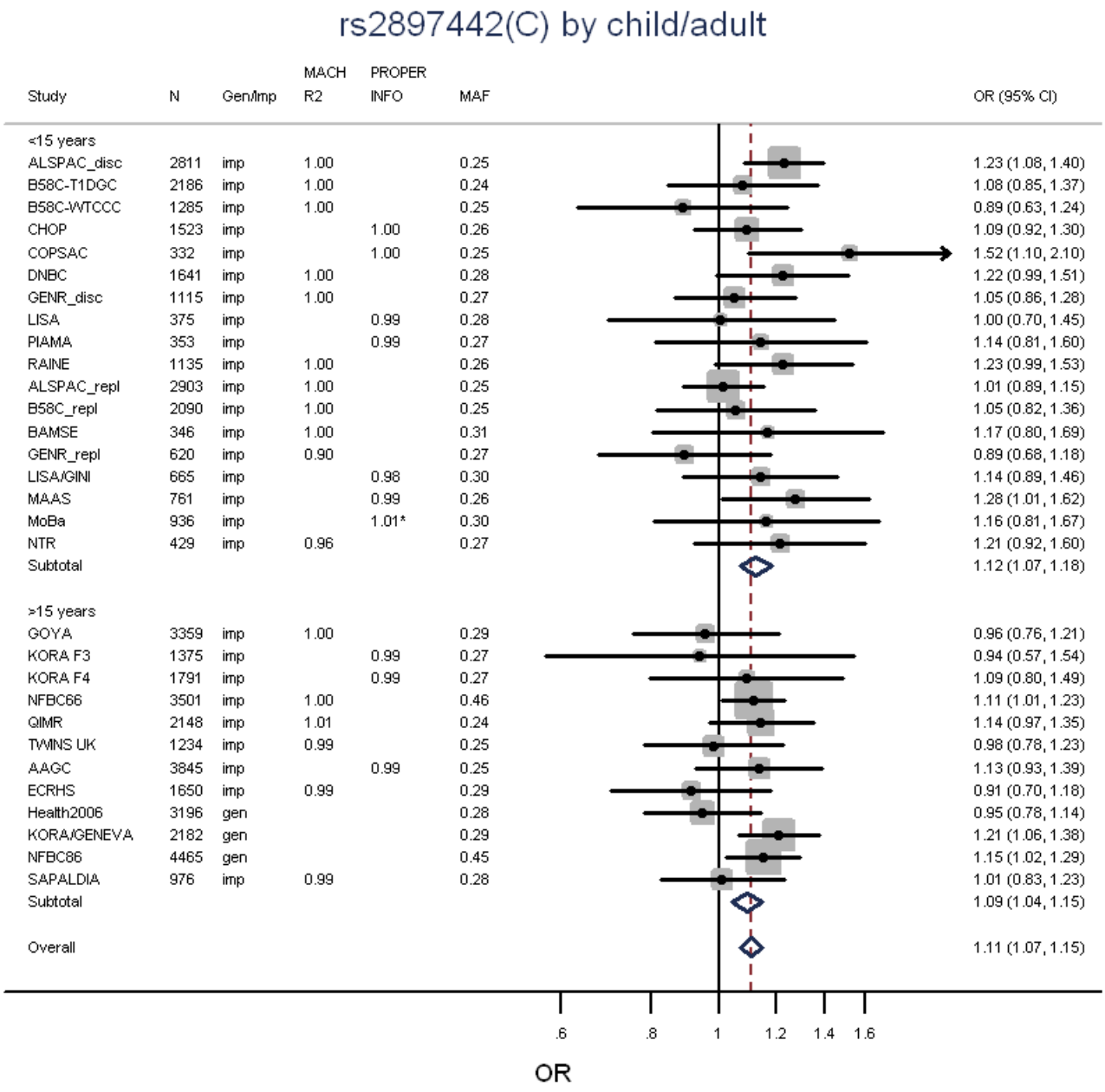
*CHOP used sub-optimal ICD9 diagnosis in medical record to identify cases. Reported physician's AD diagnosis subgroup result with CHOP excluded: OR=1.06 (95%CI 0.94 - 1.19).

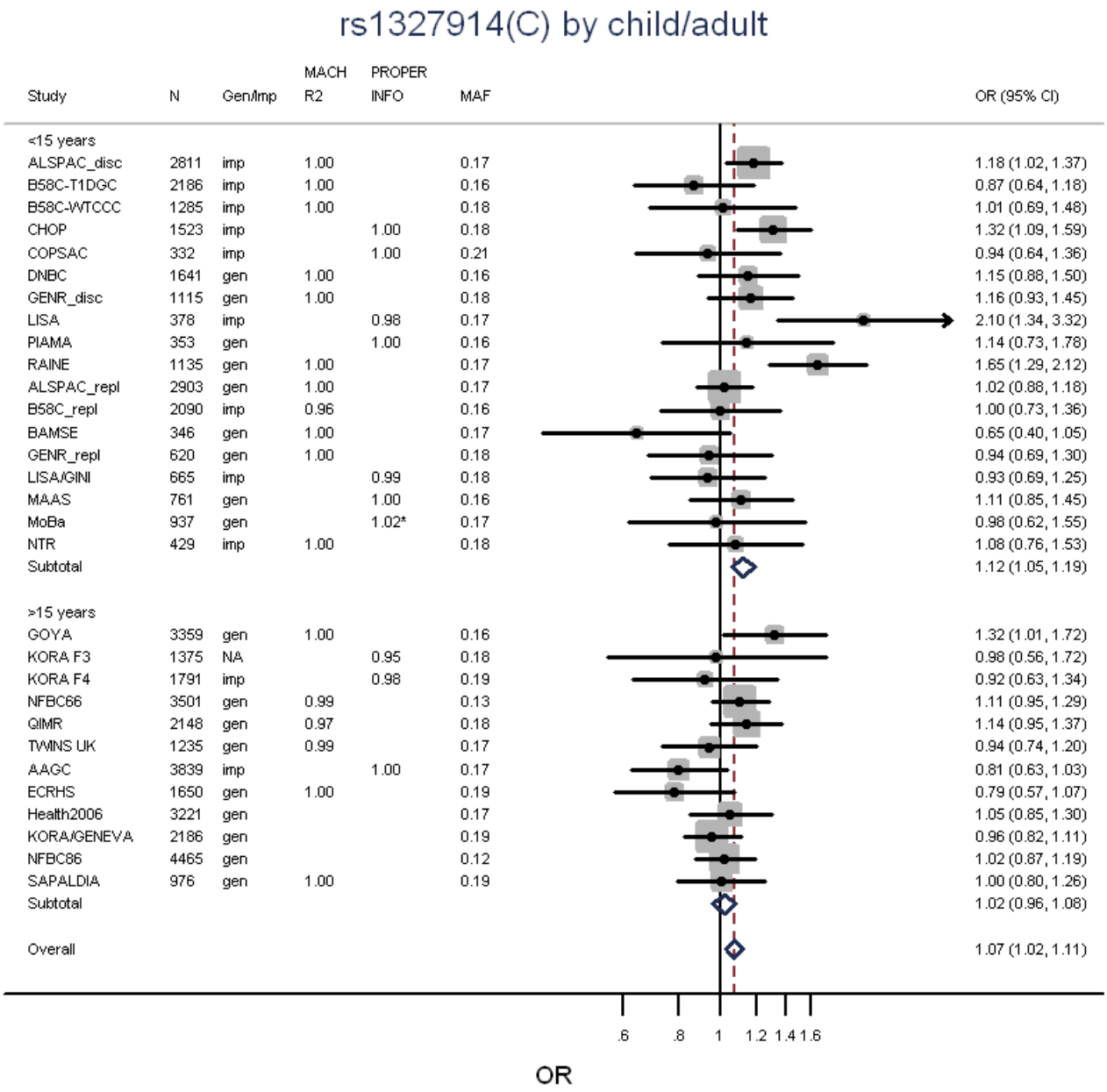
b. diagnosis before the age of 15 (child) versus up to and including adults. Difference between subgroup p-values: rs479844 p=0.224; rs2164983 p=0.037; rs2897442 p=0.465; rs1327914 p=0.028; rs10983837 p=0.773.

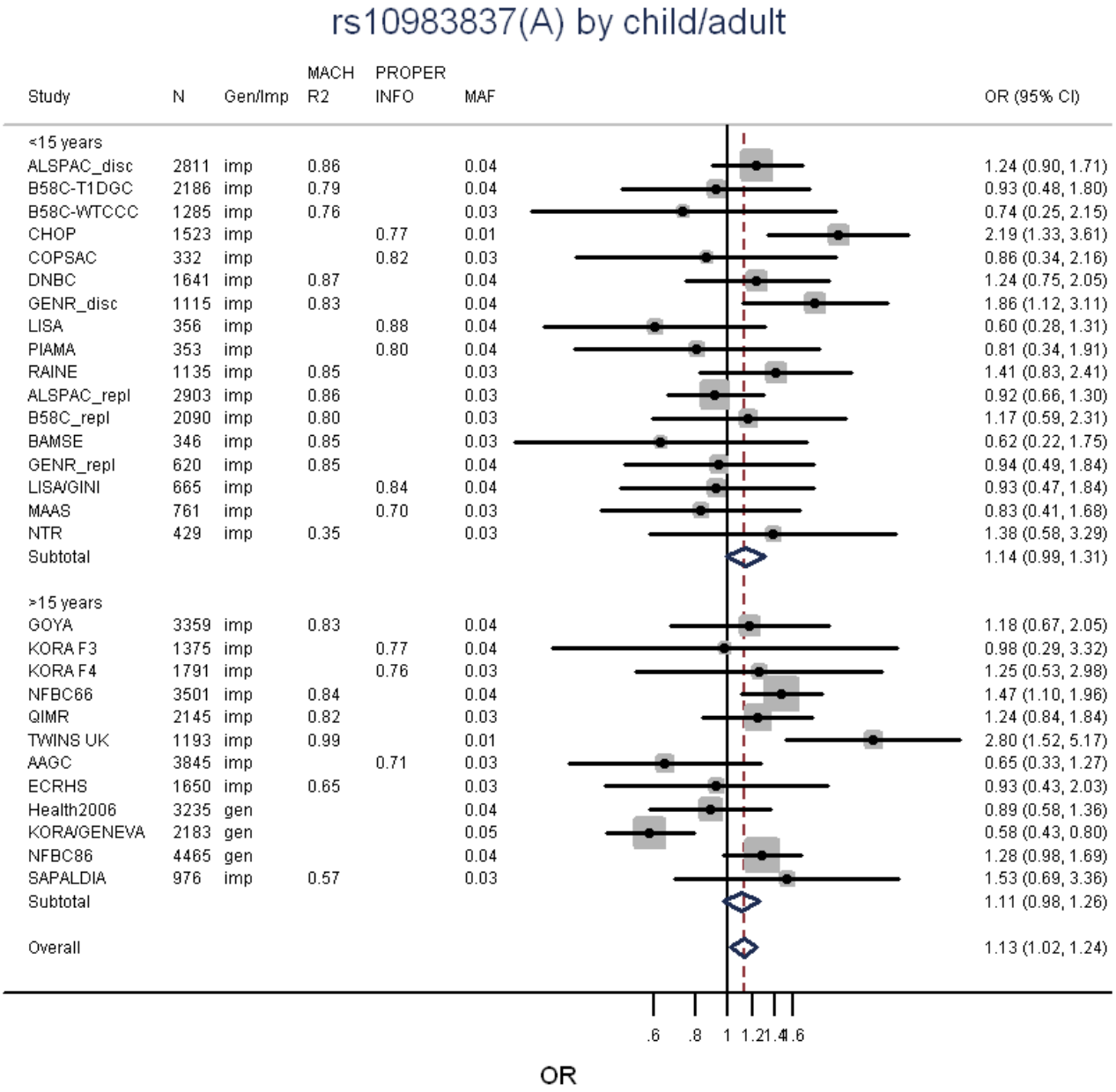


rs2164983(A) by child/adult




rs2897442(C) by child/adult
Study
N
Gen/Imp
MACH R2
PROPER INFO
MAF
OR (95% CI)
<15 years
ALSPAC_disc 2811 imp 1.00 0.25 1.23 (1.08, 1.40)
B58C-T1DGC 2186 imp 1.00 0.24 1.08 (0.85, 1.37)
B58C-WTCCC 1285 imp 1.00 0.25 0.89 (0.63, 1.24)
CHOP 1523 imp 1.00 0.26 1.09 (0.92, 1.30)
COPSAC 332 imp 1.00 0.25 1.52 (1.10, 2.10)
DNBC 1641 imp 1.00 0.28 1.22 (0.99, 1.51)
GENR_disc 1115 imp 1.00 0.27 1.05 (0.86, 1.28)
LISA 375 imp 0.99 0.28 1.00 (0.70, 1.45)
PIAMA 353 imp 0.99 0.27 1.14 (0.81, 1.60)
RAINE 1135 imp 1.00 0.26 1.23 (0.99, 1.53)
ALSPAC_repl 2903 imp 1.00 0.25 1.01 (0.89, 1.15)
B58C_repl 2090 imp 1.00 0.25 1.05 (0.82, 1.36)
BAMSE 346 imp 1.00 0.31 1.17 (0.80, 1.69)
GENR_repl 620 imp 0.90 0.27 0.89 (0.68, 1.18)
LISA/GINI 665 imp 0.98 0.30 1.14 (0.89, 1.46)
MAAS 761 imp 0.99 0.26 1.28 (1.01, 1.62)
MoBa 936 imp 1.01* 0.30 1.16 (0.81, 1.67)
NTR 429 imp 0.96 0.27 1.21 (0.92, 1.60)
Subtotal 1.12 (1.07, 1.18)
>15 years
GOYA 3359 imp 1.00 0.29 0.96 (0.76, 1.21)
KORA F3 1375 imp 0.99 0.27 0.94 (0.57, 1.54)
KORA F4 1791 imp 0.99 0.27 1.09 (0.80, 1.49)
NFBC66 3501 imp 1.00 0.46 1.11 (1.01, 1.23)
QIMR 2148 imp 1.01 0.24 1.14 (0.97, 1.35)
TWINS UK 1234 imp 0.99 0.25 0.98 (0.78, 1.23)
AAGC 3845 imp 0.99 0.25 1.13 (0.93, 1.39)
ECRHS 1650 imp 0.99 0.29 0.91 (0.70, 1.18)
Health2006 3196 gen 0.28 0.95 (0.78, 1.14)
KORA/GENEVA 2182 gen 0.29 1.21 (1.06, 1.38)
NFBC86 4465 gen 0.45 1.15 (1.02, 1.29)
SAPALDIA 976 imp 0.99 0.28 1.01 (0.83, 1.23)
Subtotal 1.09 (1.04, 1.15)
Overall 1.11 (1.07, 1.15)
.6
.8
1
1.2
1.4
1.6
OR


rs1327914(C) by child/adult
Study
N
Gen/Imp
MACH R2
PROPER INFO
MAF
OR (95% CI)
<15 years
ALSPAC_disc 2811 imp 1.00 0.17 1.18 (1.02, 1.37)
B58C-T1DGC 2186 imp 1.00 0.16 0.87 (0.64, 1.18)
B58C-WTCCC 1285 imp 1.00 0.18 1.01 (0.69, 1.48)
CHOP 1523 imp 1.00 0.18 1.32 (1.09, 1.59)
COPSAC 332 imp 1.00 0.21 0.94 (0.64, 1.36)
DNBC 1641 gen 1.00 0.16 1.15 (0.88, 1.50)
GENR_disc 1115 gen 1.00 0.18 1.16 (0.93, 1.45)
LISA 378 imp 0.98 0.17 2.10 (1.34, 3.32)
PIAMA 353 gen 1.00 0.16 1.14 (0.73, 1.78)
RAINE 1135 gen 1.00 0.17 1.65 (1.29, 2.12)
ALSPAC_repl 2903 gen 1.00 0.17 1.02 (0.88, 1.18)
B58C_repl 2090 imp 0.96 0.16 1.00 (0.73, 1.36)
BAMSE 346 gen 1.00 0.17 0.65 (0.40, 1.05)
GENR_repl 620 gen 1.00 0.18 0.94 (0.69, 1.30)
LISA/GINI 665 imp 0.99 0.18 0.93 (0.69, 1.25)
MAAS 761 gen 1.00 0.16 1.11 (0.85, 1.45)
MoBa 937 gen 1.02* 0.17 0.98 (0.62, 1.55)
NTR 429 imp 1.00 0.18 1.08 (0.76, 1.53)
Subtotal 1.12 (1.05, 1.19)
>15 years
GOYA 3359 gen 1.00 0.16 1.32 (1.01, 1.72)
KORA F3 1375 NA 0.95 0.18 0.98 (0.56, 1.72)
KORA F4 1791 imp 0.98 0.19 0.92 (0.63, 1.34)
NFBC66 3501 gen 0.99 0.13 1.11 (0.95, 1.29)
QIMR 2148 gen 0.97 0.18 1.14 (0.95, 1.37)
TWINS UK 1235 gen 0.99 0.17 0.94 (0.74, 1.20)
AAGC 3839 imp 1.00 0.17 0.81 (0.63, 1.03)
ECRHS 1650 gen 1.00 0.19 0.79 (0.57, 1.07)
Health2006 3221 gen 0.17 1.05 (0.85, 1.30)
KORA/GENEVA 2186 gen 0.19 0.96 (0.82, 1.11)
NFBC86 4465 gen 0.12 1.02 (0.87, 1.19)
SAPALDIA 976 gen 1.00 0.19 1.00 (0.80, 1.26)
Subtotal 1.02 (0.96, 1.08)
Overall 1.07 (1.02, 1.11)
.6
.8
1
1.2
1.4
1.6
OR


rs10983837(A) by child/adult
Study N Gen/Imp MACH R2 PROPER INFO MAF OR (95% CI)
<15 years
ALSPAC_disc 2811 imp 0.86 0.04 1.24 (0.90, 1.71)
B58C-T1DGC 2186 imp 0.79 0.04 0.93 (0.48, 1.80)
B58C-WTCCC 1285 imp 0.76 0.03 0.74 (0.25, 2.15)
CHOP 1523 imp 0.77 0.01 2.19 (1.33, 3.61)
COPSAC 332 imp 0.82 0.03 0.86 (0.34, 2.16)
DNBC 1641 imp 0.87 0.04 1.24 (0.75, 2.05)
GENR_disc 1115 imp 0.83 0.04 1.86 (1.12, 3.11)
LISA 356 imp 0.88 0.04 0.60 (0.28, 1.31)
PIAMA 353 imp 0.80 0.04 0.81 (0.34, 1.91)
RAINE 1135 imp 0.85 0.03 1.41 (0.83, 2.41)
ALSPAC_repl 2903 imp 0.86 0.03 0.92 (0.66, 1.30)
B58C_repl 2090 imp 0.80 0.03 1.17 (0.59, 2.31)
BAMSE 346 imp 0.85 0.03 0.62 (0.22, 1.75)
GENR_repl 620 imp 0.85 0.04 0.94 (0.49, 1.84)
LISA/GINI 665 imp 0.84 0.04 0.93 (0.47, 1.84)
MAAS 761 imp 0.70 0.03 0.83 (0.41, 1.68)
NTR 429 imp 0.35 0.03 1.38 (0.58, 3.29)
Subtotal 1.14 (0.99, 1.31)
>15 years
GOYA 3359 imp 0.83 0.04 1.18 (0.67, 2.05)
KORA F3 1375 imp 0.77 0.04 0.98 (0.29, 3.32)
KORA F4 1791 imp 0.76 0.03 1.25 (0.53, 2.98)
NFBC66 3501 imp 0.84 0.04 1.47 (1.10, 1.96)
QIMR 2145 imp 0.82 0.03 1.24 (0.84, 1.84)
TWINS UK 1193 imp 0.99 0.01 2.80 (1.52, 5.17)
AAGC 3845 imp 0.71 0.03 0.65 (0.33, 1.27)
ECRHS 1650 imp 0.65 0.03 0.93 (0.43, 2.03)
Health2006 3235 gen 0.04 0.89 (0.58, 1.36)
KORA/GENEVA 2183 gen 0.05 0.58 (0.43, 0.80)
NFBC86 4465 gen 0.04 1.28 (0.98, 1.69)
SAPALDIA 976 imp 0.57 0.03 1.53 (0.69, 3.36)
Subtotal 1.11 (0.98, 1.26)
Overall 1.13 (1.02, 1.24)
.6 .8 1 1.2 1.4 1.6
OR

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