Published in final edited form as:
Nat Genet. 2007 November ; 39(11): 1329–1337. doi:10.1038/ng.2007.17.

Association scan of 14,500 nsSNPs in four common diseases identifies variants involved in autoimmunity

WTCCC
TASC

Abstract

We have genotyped 14,436 nsSNPs and 897 MHC tagSNPs in 1000 independent cases of Ankylosing Spondylitis (AS), Autoimmune Thyroid Disease (AITD), Multiple Sclerosis and Breast Cancer. Comparing each of these diseases against a common control set of 1500 unselected healthy British individuals, we report initial association and independent replication of two new loci for AS, *ARTS1* and *IL23R*, and confirmation of the previously reported AITD association with *TSHR* and *FCRL3*. These findings, enabled in part by expanding the control reference group with individuals from the other disease groups to increase statistical power, highlight important new possibilities for autoimmune regulation and suggest that IL23R may be a common susceptibility factor for the major 'seronegative' diseases.

Genome-wide association scans are currently revealing a number of new genetic variants for common diseases; eg1-11. We have recently completed the largest and most comprehensive scan conducted to date, involving genome-wide association studies of 2000 individuals from each of seven common disease cohorts and 3000 common control individuals using a dense panel of >500k markers12. In parallel with this scan, we conducted a study of 5,500 independent individuals with a genome-wide set of non-synonymous coding variants, an approach which has recently yielded new findings for Type 1 diabetes and Crohn's disease and which has been proposed as an efficient complementary approach to whole genome scans13-15. Here we report several new replicated associations in our scan of nsSNPs in 1500 shared controls and 1000 individuals from each of 4 different diseases: Ankylosing Spondylitis (AS), Autoimmune Thyroid Disease/Graves' Disease (AITD), Breast Cancer (BC) and Multiple Sclerosis (MS).

RESULTS

Initial genotyping was performed with a custom-made Infinium array (Illumina) and involved 14,436 nsSNPs (assays were synthesized for 16,078 nsSNPs). At the time of study inception, this comprised the complete set of experimentally validated nsSNPs with MAF > 1% in Caucasian samples. In addition, because three of the diseases were of autoimmune aetiology, we also typed a dense set of 897 SNPs throughout the major histocompatibility complex (MHC) which together with 348 nsSNPs in this region provided comprehensive tag SNP coverage ($r^2 \geq 0.8$ with all SNPs in ref[16]). Finally, 103 SNPs were typed in pigmentation genes specifically designed to differentiate between population groups. Similar

Address Correspondence to: Lon R. Cardon[1,2] or David M. Evans[2]. [1]Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, Seattle, Washington, 98109, USA. Tel: +1 206 667 6542. Fax: +1 206 667 4023. Email: lcardon@fhcrc.org.
[2]University of Oxford, Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7BN Tel: +44 (0)1865 287 587, Fax: +44 (0)1865 287 697. Email: davide@well.ox.ac.uk.
List of participants and affiliations appear at the end of this manuscript

Membership of the BRAGGS and Breast Cancer Susceptibility Collaboration (UK) is listed in the Supplementary Information.

Europe PMC Funders Author Manuscripts

to previous studies, our data revealed that detailed assessment of initial data is critically important to the process of association inference, as biases in genotype calling lead to clear inflation of false positive rates[12,17]. This inflation is exaggerated in nsSNP data because they tend to have lower allele frequencies than otherwise anonymous genomic SNPs and genotype calling is often most difficult for rare alleles. If only cursory filtering had been applied in the present case, a large number of striking false-positives would have emerged (Supplementary Figures 1-4). Table 1 displays the total number of SNPs and individuals remaining after genotype and sample quality control procedures (see Methods).

Association with the MHC

The strongest associations observed in the study were between SNPs in the MHC region and the three auto-immune diseases studied, AS, AITD and MS, with p-values of $<10^{-20}$ for each disease (Figure 1). No association of the MHC was seen with BC ($p > 10^{-4}$ across the region). For each of the autoimmune diseases, the maximum signal is centered around the known HLA-associated genes (ie, HLA-B in AS, HLA-DRB1 in MS and the MHC Class I-II for AITD), but in all cases it extends far beyond the specific associated haplotype(s). For example, in AS, association was observed at $p < 10^{-20}$ across ~ 1.5 Mb. Given the well-known large effect of B27 with AS (odds ratio 100-200 in most populations), the extent of this association signal reflects the fact that with such large effects, even very distant SNPs in modest LD will reveal indirect evidence for association. Strong signals like these may also cloud the evidence for additional HLA loci18. Disentangling similar patterns of association within the MHC has proven extremely challenging in the past and will be addressed in future studies of these data. Here we focus specifically on the nsSNP results.

Association with nsSNPs

A major advantage of the WTCCC design is the availability of multiple disease cohorts which are similar in terms of ancestry and which have been typed on the same genetic markers12,17. Assuming that each disease has at least some genetic loci that differ between diseases, it should be possible to increase power to detect association by combining the other three case groups with the 58C controls19. For each disease we therefore conducted two primary analyses: (1) testing nsSNP associations for each disease against the 1958 Birth Cohort controls (58C); and (2) testing the same associations for each disease against an expanded reference group comprising the combined cases from the other three disease groups plus individuals from the 58C. A similar set of analyses was conducted for each of the autoimmune disorders against a reference group comprising 58C+BC, but the results were very similar to those for the fully expanded groups so here we describe the larger sample (see Supplementary Table 1). In addition, since it is possible that different autoimmune diseases share similar genetic etiologies, we also compared a combined AS, AITD and MS group against the combined set of BC patients and 58C controls. All of our analyses are reported without regard to specific treatment of population structure, as the degree of structure in our final genotype data is not severe (Genomic Control20 $\lambda = 1.07$ to 1.13 in the 58C-only datasets; $\lambda = 1.03$ to 1.06 in the expanded reference group comparisons, see Table 2), consistent with our recent findings from 17,000 UK individuals involving the same controls12.

nsSNP association results (i.e. excluding the MHC region) for each of the four disease groups against the 58C controls are shown in Figure 2 and Table 3. Two SNPs on chromosome 5 reached a high-level of statistical significance for AS (rs27044: $p = 1.0 \times 10^{-6}$; rs30187: $p = 3.0 \times 10^{-6}$). This level of significance exceeds the 10^{-5}-10^{-6} thresholds advocated for gene-based scans21, as well as the oft-used Bonferroni correction at $p< 0.05$ (see refs12,21 for a discussion of genome-wide association significance). Both of these markers reside in the gene for *ARTS1* (*ERAAP, ERAP1*), a type II integral transmembrane

aminopeptidase with diverse immunological functions. Four additional SNPs display significance at $p < 10^{-4}$, with an increasing number of possible associations at more modest significance levels. Several of the more strongly associated SNPs or others in the same genes have previously been associated with the particular disease, and for others there exists functional evidence for their involvement in the particular condition. These include SNPs in the genes *FCRL3* and *FCRL5* in the case of AITD, *IL23R* in the case of AS, *MEL-18* in the case of BC, and *IL7R* for MS. The complete list of single-marker association results is provided in Supplementary Table 1.

The results for analyses involving the expanded reference group are presented in Supplementary Figure 5 and Supplementary Table 1. Many of the SNPs that showed moderate to strong evidence for association in the initial analysis revealed substantially increased significance with the larger reference group. Notably, these included the SNPs rs27044 ($p = 4.0 \times 10^{-8}$) and rs30187 ($p = 2.1 \times 10^{-7}$) in *ARTS1*, as well as several other variants in this gene. A second SNP, rs7302230 in the Calsyntenin-3 gene on chromosome 12, showed substantially stronger evidence for association in the expanded reference group analysis ($p = 5.3 \times 10^{-7}$) relative to the 58C-only results ($p = 1.1 \times 10^{-4}$). Results of the expanded group also showed elevated results for several SNPs which did not appear exceptional in the original (non-combined) analyses, including SNPs in several candidate genes such as sialoadhesin22 and complement receptor 1 for AS, *PIK3R2* for MS, and *C8B*, *IL17R* and *TYK2* in the combined autoimmune disease analysis. SNP rs3783941 in the thyroid stimulating hormone receptor (*TSHR*) gene emerged as amongst the most significant in the expanded reference group analyses of AITD ($p = 2.1 \times 10^{-5}$). Several polymorphisms in the *TSHR* have previously been associated with Graves' disease23,24. This known association did not reach even the modest significance level of 10^{-3} in the original analyses, but adding an additional 3000 further reference samples delineated it from the background noise and further supports the original independent report.

ARTS1 association confirmed in an independent cohort

In order to validate the most exceptional findings from the initial study, we genotyped the *ARTS1*, *CLSTN3* and *LNPEP* SNPs in 471 independent AS cases and 625 new controls (all North American Caucasian). Table 4 shows the results of the genes examined for AS. The data strongly suggest that the *ARTS1* association is genuine. All *ARTS1* nsSNPs reveal independent replication in the same direction of effect, with replication significance levels ranging from 4.7×10^{-4} to 5.1×10^{-5}. When combined with the original samples, the results reveal striking evidence for association with AS ($p = 1.2 \times 10^{-8}$ to 3.4×10^{-10}). The population attributable risk25 contributed by the most strongly associated marker in the North American dataset (rs2287987) is 26%.

Association was also confirmed with marker rs2303138 in the *LNPEP* gene, which lies 127kb 3′ of *ARTS1*. This marker is in strong LD with *ARTS1* markers (D' = 1, rs27044 - rs2303138). We tested the interdependence of the *ARTS1* and *LNPEP* associations using conditional logistic regression. The remaining association at *LNPEP* is weak after controlling for *ARTS1* ($p = 0.01$), whereas the association at *ARTS1* remains strong after controlling for *LNPEP* ($p = 2.7 \times 10^{-6}$), suggesting that the *LNPEP* association may only be secondary to LD with a true association at *ARTS1*.

No association was seen with *CLSTN3* in the confirmation set. The US controls exhibited the same allele frequency as the UK controls (5%) but the allele frequency in the US cases was less than that of the UK cases (6% vs 8%), suggesting no association in the US samples and substantially reducing the significance of the combined data. Calystenin-3 is a post-synaptic neuronal membrane protein, and is an unlikely candidate gene for involvement in inflammatory arthritis. The failure to replicate this association suggests that our replication

sample size is insufficient to detect the modest effect or it was a false positive in the initial scan.

IL23R variants confer risk of AS

The *IL23R* variant rs11209026, whilst not striking in the initial nsSNP scan ($p = 1.7 \times 10^{-3}$), is of particular interest as it was recently associated with both Crohn's Disease26,27 and psoriasis28, conditions which commonly co-occur with AS. To better define this association, 7 additional SNPs in *IL23R* were genotyped in the same 1000 British AS cases and 1500 58C controls as well as the North American Caucasian replication samples (Table 4). In the WTCCC dataset, strong association was seen in 7 of 8 genotyped SNPs ($p \leq 0.008$, including the original nsSNP rs11209026), with the strongest association seen at rs11209032 ($p = 2.0 \times 10^{-6}$). In the replication dataset, association was observed with all genotyped SNPs ($p \leq 0.04$), with peak association observed with marker rs10489629 ($p = 4.2 \times 10^{-5}$). In the combined dataset, the strongest association observed was with SNP rs11209032 (odds ratio 1.3, 95% CI 1.2 - 1.4, $p = 7.5 \times 10^{-9}$). The attributable risk for this marker in the replication cohort is 9%. Conditional logistic regression analyses did not reveal a single primary disease-associated marker, with residual association remaining after having controlled for association at the remaining SNPs. Considering only AS cases who self-reported as not having inflammatory bowel disease (n = 1066) the association remained strong and was still strongest at rs11209032 ($p = 6.9 \times 10^{-7}$), indicating that there is a primary association with AS and that the observed association was not due to coexistent clinical inflammatory bowel disease.

In contrast to the pleiotropic effects of *IL23R*, the *ARTS1* association evidence appears confined to AS. We genotyped the five AS-associated SNPs in 755 British Crohn's disease and 1011 ulcerative colitis cases, and 633 healthy controls. No association was seen with either UC or CD (Armitage trend $p > 0.4$ for all markers).

FCRL3 confirmed in AITD pathogenesis

In addition to the AS replications, we attempted to confirm and extend the *FCRL3* association in AITD. The SNP rs7522061 in the *FCRL3* gene was recently reported to be associated with AITD29 and two other autoimmune diseases, rheumatoid arthritis and systemic lupus erythematosus30. Our initial association evidence ($p = 2.1 \times 10^{-4}$) likely reflects the signal of the originally detected polymorphism since the level of linkage disequilibrium (LD) is high across this gene. In fact, the entire 1q21-q23 region (which includes another gene, *FCRL5*, flagged in our scan) has also been implicated in several autoimmune diseases including psoriasis and multiple sclerosis31,32.

On the basis of the original findings on 1q21-q23, the original cohort was increased from 1,000 to 2,500 Graves Disease (GD) cases and we used 2,500 different 1958 cohort controls. Eight SNPs that tagged the *FCRL3* and *FCRL5* gene regions were selected and typed in all 5,000 samples using an alternative genotyping platform. SNP rs3761959, which tags rs7522061 and rs7528684 (previously associated with RA and GD), was associated with GD in this extended cohort (Table 5), therefore, confirming the original result. In total, three of the seven *FCRL3* SNPs showed some evidence for association ($p < .05$) with SNP rs11264798 being the most associated of the tag SNPs, $p = 4.0 \times 10^{-3}$. SNP rs6667109 in *FCRL5*, which tagged SNPs rs6427384, rs2012199 and rs6679793, all found to be weakly associated in the original study, showed little evidence of association in this extended cohort.

DISCUSSION

Our scan of nsSNPs has identified and validated two new genes for AS (*ARTS1* and *IL23R*), confirmed and extended markers in the *TSHR* and *FCRL3* genes which have previously been associated with AITD, and provided a dense set of association data for AITD, AS and MS across the MHC region. The challenge now is to design functional studies that will reveal how variation in these genes translates into physiological processes that influence disease risk.

From a functional perspective, the *ARTS1* and *IL23R* genes represent excellent biological candidates. *ARTS1* has two known functions, either of which may explain its association with AS. Within the endoplasmic reticulum, ARTS1 is involved in trimming peptides to the optimal length for MHC Class I presentation33,34. AS is primarily an HLA Class I mediated autoimmune disease35, with >90% of cases carrying the HLA-B27 allele. How B27 increases risk of AS is unknown, but if the mechanism of association of *ARTS1* with the disease is through effects on peptide presentation, this would inform research into the mechanism explaining the association of B27 with AS. The second known function of ARTS1 is that it cleaves cell surface receptors for the pro-inflammatory cytokines IL-1 (IL-1R2)36, IL-6 (IL-6Rα)37 and TNF (TNFR1)38, thereby downregulating their signaling. Genetic variants that alter the functioning of ARTS1 could therefore have pro-inflammatory effects through this mechanism.

As well as AS, polymorphisms in *IL23R* have been recently documented in Crohn's Disease 26,27 and psoriasis 28, suggesting that this gene is a common susceptibility factor for the major 'seronegative' diseases, at least partially explaining their co-occurrence. IL-23R is a key factor in the regulation of a newly defined effector T-cell subset, T_H17 cells. T_H17 cells were originally identified as a distinct subset of T-cells expressing high levels of the pro-inflammatory cytokine IL-17 in response to stimulation, in addition to IL-1, IL-6, TNFa, IL-22 and IL-25 (IL-17E). IL-23 has been shown to be important in the mouse models experimental autoimmune encephalomyelitis39, collagen-induced arthritis40 and mouse models of inflammatory bowel disease41, but has not been studied in AS, either in humans or animal models of disease. These studies show that blocking IL-23 reduces inflammation in these models, suggesting that the *IL23R* variants associated with disease are pro-inflammatory. Successful treatment of Crohn's disease has been reported with anti-IL-12p40 antibodies, which block both IL-12 and IL-23, as these cytokines share the IL-12p40 chain42. No functional studies of *IL23R* variants have been reported to date, and it is unclear to what extent findings in studies targeting IL-23 can be generalised to mechanisms by which *IL23R* variation affects disease susceptibility. Our genetic findings provide a major novel insight into the aetiopathogenesis of AS, and suggest that treatments targeting IL-23 may prove effective in this condition, but clearly much more needs to be understood about the mechanism underlying the observed association.

Despite the successful identification of the *ARTS1* and *IL23R* genes, it is likely that additional real associations are either present in our data but with modest effect sizes, or that our focus on non-synonymous coding changes led us to miss real genes. For example, we found no evidence for association at even a nominal $p < 0.05$ in or within 2 Mb of the recently reported and validated breast cancer gene *FGFR3*3,43 (2 nsSNPs in FGFR3 were included in our panel, rs1078816 and rs755793; the former yielded $p = 0.12$ and the latter was monomorphic in these samples), nor in or near any of the other suggestive breast cancer genes reported in refs[3,43]. Lack of statistical power in 1000 cases and 1500 controls is a likely contributor to this lack of replication, but some of these loci, notably *FGFR3*, appear to be intronic and thus would likely have been missed even with larger samples.

The issue of statistical power is emphasized in studies of non-synonymous coding changes, which have a greater number of rare variants than other genetic variants and thus will require even larger sample sizes unless the effect sizes are larger. Other analytical approaches, such as assessing evidence for association between clusters of rare variants rather than individual loci may prove highly informative in this regard44, but most of the nsSNPs available in this study exist either by themselves in each gene or with 1-2 others, which precludes these assessments (Supplementary Figure 6). In our analyses, *ARTS1* was the only locus showing exceptional statistical significance in the scan of 1000 cases and 1500 controls, thus emphasizing the need for greater statistical power. We increased power by expanding the controls, or 'reference set', to include some or all of the other disease samples. In doing so, *ARTS1* showed strong association evidence, the *IL23R* SNPs increased to a level that began to delineate them from background noise, and the AITD/*TSHR* confirmation emerged. This demonstration of increased statistical power by combining multiple datasets is timely given the international impetus to make genotype data available to the scientific community. Future investigations will be needed to assess the power vs confounding effects and the statistical corrections needed to combine more heterogeneous samples from broader sampling regions.

These results also highlight the question of how much information may be missed by focusing on coding SNPs rather than searching more broadly over the genome at large. This question is relevant because the trade-off between SNP panel selection and sample size to genotype is a salient factor in every genome-wide study design. In the HapMap data45, a substantial portion of the common non-synonymous variation in our nsSNP set is captured by available genome-wide panels (about 65% of common (MAF > 5%) nsSNPs in the Illumina Human NS-12 Beadchip are tagged with an $r^2 > .8$ using the Affymetrix 500K chip, rising to 90% for the Illumina HumanHap300 which includes almost all of the nsSNPs from the NS-12 Beadchip). The four primary associated variants flagged in our study (i.e., in *ARTS1, IL23R, TSHR* and *FCRL3*) would have been detected using any of the genome-wide panels, since either the markers themselves or a SNP in high LD with them ($r^2 \geq .78$), are present on the genome-wide chips. This LD relationship also emphasizes the fact that observing an association with a nsSNP does not necessarily imply that the nsSNP is causal, as it may be indirectly associated with other genetic variants in or outside the gene. Given this high degree of overlap, the continuously increasing coverage of many available genotyping products and concomitant pressures to decrease assay costs, these data suggest that future gene-centric scans will be efficiently subsumed by the more encompassing and less hypothesis-driven genome-wide SNP panels.

METHODS

Subjects

Individuals included in the study were self-identified as white Europeans and came from mainland UK (England, Scotland and Wales, but not Northern Ireland). The 1500 control samples were from the British 1958 Birth Cohort (58C, also known as the National Child Development Study), which included all births in England, Wales and Scotland during one week in 1958. Recruitment details and diagnostic criteria for each of the four case groups and the 58C are further described in the Supplementary Methods online.

Sample QA/QC

Genome-wide Identity by State (IBS) sharing was calculated for each pair of individuals in the combined sample of cohorts in order to identify first and second degree relatives that might contaminate the study. One subject from any pair of individuals who shared < 400 genotypes IBS = 0 and/or > 80% alleles IBS was removed from all subsequent analyses (i.e.

the individual with the most missing genotypes). In order to identify individuals who might have ancestries other than Western European, we merged each of our cohorts with the 60 CEU founder, 60 YRI founder, and 90 JPT and CHB individuals from the International HapMap Project45. We calculated genome-wide identity by state distances for each pair of individuals (i.e. one minus average IBS sharing) on those markers shared between HapMap and our non-synonymous panel, and then used the multidimensional scaling option in R to generate a two dimensional plot based upon individuals' scores on the first two principal coordinates from this analysis (Supplementary Figure 2). Any WTCCC sample that was not present in the main cluster with the CEU individuals was excluded from subsequent analyses. Finally, any individual with >10% of genotypes missing was removed from the analysis. The number of individuals remaining after these quality control measures is displayed in Table 1.

Genotyping

We genotyped a total of 14,436 nsSNPs across the genome on all case and control samples. Because three of the diseases were of autoimmune etiology, we also typed an additional 897 SNPs within the MHC region, as well as 103 SNPs in pigmentation genes specifically designed to differentiate between population groups. SNP genotyping was performed with the Infinium I assay (Illumina) which is based on Allele Specific Primer Extension (ASPE) and the use of a single fluorochrome. The assay requires ~250 ng of genomic DNA which is first subjected to a round of isothermal amplification generating a "high complexity" representation of the genome with most loci represented at usable amounts. There are two allele specific probes (50mers) per SNP each on a different bead type; each bead type is present on the array 30 times on average (minimum 5), allowing for multiple independent measurements. We processed six samples per array. Clustering was performed with the GenCall software version 6.2.0.4 which assigns a quality score to each locus and an individual genotype confidence score (GC score) which is based on the distance of a genotype from the centre of the nearest cluster. First, we removed samples with more than 50% of loci having a score below 0.7 and then all loci with a quality score below 0.2. Post clustering we applied two additional filtering criteria: (i) omit individual genotypes with a GC score < 0.15 and (ii) remove any SNP which had more than 20% of its samples with GC scores below 0.15. The above criteria were designed so as to optimize genotype accuracy whilst minimizing uncalled genotypes.

Statistical Analysis

Markers that were monomorphic in both case and control samples, SNPs with > 10% missing genotypes, and SNPs with differences in the amount of missing data between cases and controls ($p < 10^{-4}$ as assessed by χ^2 test) were excluded from all analyses involving that case group only. In addition any marker which failed an exact test of Hardy-Weinberg equilibrium in controls ($p < 10^{-7}$) was excluded from all analyses46.

Cochran-Armitage Tests for trend47 were conducted using the PLINK program48. For the present analyses, we used the significance thresholds of $p < 10^{-4} – 10^{-6}$, as suggested for gene-based scans with stronger prior probabilities than scans of anonymous markers21. In the present context, the lower thresholds are similar to Bonferroni significance levels (Bonferroni-corrected p = .05 corresponds to nominal $p = 3 \times 10^{-6}$). The conditional logistic regression analyses involving the *LNPEP* and *ARTS1* SNPs were performed using Purcell's WHAP program49.

We manually rechecked the genotype calls of every nsSNP with an asymptotic significance level of $p < 10^{-3}$ by inspecting raw signal intensity values and their corresponding automated genotype calls. Interestingly, this flagged an additional 33 markers with clear problems in

Europe PMC Funders Author Manuscripts

genotype calling, which were subsequently excluded from all analyses (see Supplementary Figure 4 for an example). These results indicate that this genotyping platform generally yields highly accurate genotypes, but errors do occur and they can be distributed non-randomly between cases and controls despite stringent QC procedures. It is imperative to check the clustering of the most significant SNPs to ensure that evidence for associations are not a result of genotyping error.

Whilst great lengths were taken to ensure our samples were as homogenous as possible in terms of genetic ancestry, even subtle population substructure can substantially influence tests of association in large genome-wide analyses involving thousands of individuals50. We therefore calculated the genomic-control inflation factor, $\lambda 20$, for each case-control sample as well as in the analyses where we combined the other case groups with the control individuals (Table 2). In general, values for λ were small (~1.1) indicating a small degree of substructure in UK samples which induces only a slight inflation of the test statistic under the null hypothesis, consistent with the results from our companion paper12. We, therefore, present uncorrected results in all analyses reported.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank all the patients and controls who participated in this study.

AITD: We wish to thank the collection coordinators, Jackie Carr-Smith and all contributors to the AITD national DNA collection of index cases and family members from centres including Birmingham, Bournemouth, Cambridge, Cardiff, Exeter, Leeds, Newcastle and Sheffield. Principle leads for the AITD UK national collection are: Simon HS Pearce (Newcastle), Bijay Vaidya (Exeter), John H Lazarus (Cardiff), Amit Allahabadia (Sheffield), Mary Armitage (Bournemouth), Peter J Grant (Leeds), VK Chatterjee (Cambridge).

AS: We wish to thank the Arthritis Research Campaign (UK). MAB is funded by the National Health and Medical Research Council (Australia). TASC is funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases grants 1PO1-052915-01,RO1 AR046208, and RO1-AR048465,as well as by University of Texas at Houston CTSA grant UL1RR024148, Cedars-Sinai GCRC grant MO1-RR00425, The Rosalind Russell Center for Arthritis Research at The University of California San Francisco, and the Intramural Research Program, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH. We thank Rui Jin for technical assistance and Laura Diekman, Lori Guthrie, Felice Lin and Stephanie Morgan for their study coordination.

BC: The Breast Cancer samples were clinically and molecularly curated with the assistance of Anthony Renwick, Anita Hall, Anna Elliot, Hiran Jayatilake, Tasnim Chagtai, Rita Barfoot, Patrick Kelly and Katarina Spanova. Our research is supported by US Army Medical Research and Material Command grant #W81XWH-05-1-0204, The Institute of Cancer Research and Cancer Research UK.

MS: Our work has been supported by the Wellcome Trust (Grant Ref 057097), the Medical Research Council (UK) (Grant Ref G0000648), the Multiple Sclerosis Society of Great Britain and Northern Ireland (Grant Ref 730/02) and the National Institutes of Health (USA) (Grant Ref 049477). AG is a Postdoctoral Fellow of the Research Foundation - Flanders (FWO - Vlaanderen).

Luana Galver and Paulina Ng at Illumina and Jonathan Morrison at the Sanger Institute contributed in the design of the nsSNP array. The DNA team of the JDRF/WT DIL. Thomas Dibling, Cliff Hind, and Douglas Simpkin at the Sanger Institute for carrying out the genotyping.

We also with to thank Sheila Bingham and the WTCCC Inflammatory Bowel Disease group for genotyping the *ARTS1* markers in their replication samples.

Europe PMC Funders Author Manuscripts

*: Wellcome Trust Case Control Consortium

Management Committee: Paul R Burton[1], David G Clayton[2], Lon R Cardon[3,55], Nick Craddock[4], Panos Deloukas[5], Audrey Duncanson[6], Dominic P Kwiatkowski[3,5], Mark I McCarthy[3,7], Willem H Ouwehand[8,9], Nilesh J Samani[10], John A Todd[2], Peter Donnelly (Chair)[11]

Analysis Committee: Jeffrey C Barrett[3], Paul R Burton[1], Dan Davison[11], Peter Donnelly[11], Doug Easton[12], David M Evans[3], Hin-Tak Leung[2], Jonathan L Marchini[11], Andrew P Morris[3], Chris CA Spencer[11], Martin D Tobin[1], Lon R Cardon (Co-chair)[3,55], David G Clayton (Co-chair)[2]

UK Blood Services & University of Cambridge Controls: Antony P Attwood[5,8], James P Boorman[8,9], Barbara Cant[8], Ursula Everson[13], Judith M Hussey[14], Jennifer D Jolley[8], Alexandra S Knight[8], Kerstin Koch[8], Elizabeth Meech[15], Sarah Nutland[2], Christopher V Prowse[16], Helen E Stevens[2], Niall C Taylor[8], Graham R Walters[17], Neil M Walker[2], Nicholas A Watkins[8,9], Thilo Winzer[8], John A Todd[2], Willem H Ouwehand[8,9]

1958 Birth Cohort Controls: Richard W Jones[18], Wendy L McArdle[18], Susan M Ring[18], David P Strachan[19], Marcus Pembrey[18,20]

Bipolar Disorder (Aberdeen): Gerome Breen[21], David St Clair[21]; **(Birmingham):** Sian Caesar[22], Katharine Gordon-Smith[22,23], Lisa Jones[22]; **(Cardiff):** Christine Fraser[23], Elaine K Green[23], Detelina Grozeva[23], Marian L Hamshere[23], Peter A Holmans[23], Ian R Jones[23], George Kirov[23], Valentina, Moskivina[23], Ivan Nikolov[23], Michael C O'Donovan[23], Michael J Owen[23], Nick Craddock[23]; **(London):** David A Collier[24], Amanda Elkin[24], Anne Farmer[24], Richard Williamson[24], Peter McGuffin[24]; **(Newcastle):** Allan H Young[25], I Nicol Ferrier[25]

[1]Genetic Epidemiology Group, Department of Health Sciences, University of Leicester, Adrian Building, University Road, Leicester, LE1 7RH, UK;
[2]Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory, Department of Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge, Wellcome Trust/MRC Building, Cambridge, CB2 0XY, UK;
[3]Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK;
[55]PRESENT ADDRESS: Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, Seattle, Washington 98109 USA.
[4]Department of Psychological Medicine, Henry Welcome Building, School of Medicine, Cardiff University, Heath Park, Cardiff CF14 4XN, UK;
[5]The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK;
[6]The Wellcome Trust, Gibbs Building, 215 Euston Road, London NW1 2BE, UK;
[7]Oxford Centre for Diabetes, Endocrinology and Medicine, University of Oxford, Churchill Hospital, Oxford, OX3 7LJ, UK;
[8]Department of Haematology, University of Cambridge, Long Road, Cambridge, CB2 2PT, UK;
[9]National Health Service Blood and Transplant, Cambridge Centre, Long Road, Cambridge, CB2 2PT, UK;
[10]Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK;
[11]Department of Statistics, University of Oxford, 1 South Parks Road, Oxford OX1 3TG, UK;
[12]Cancer Research UK Genetic Epidemiology Unit, Strangeways Research Laboratory, Worts Causeway, Cambridge CB1 8RN, UK;
[13]National Health Service Blood and Transplant, Sheffield Centre, Longley Lane, Sheffield S5 7JN, UK;
[14]National Health Service Blood and Transplant, Brentwood Centre, Crescent Drive, Brentwood, CM15 8DP, UK;
[15]The Welsh Blood Service, Ely Valley Road, Talbot Green, Pontyclun, CF72 9WB, UK;
[16]The Scottish National Blood Transfusion Service, Ellen's Glen Road, Edinburgh, EH17 7QT, UK;
[17]National Health Service Blood and Transplant, Southampton centre, Coxford Road, Southampton, SO16 5AF, UK;
[18]Avon Longitudinal Study of Parents and Children, University of Bristol, 24 Tyndall Avenue, Bristol, BS8 1TQ, UK;
[19]Division of Community Health Services, St George's University of London, Crammer Terrace, London SW17 0RE, UK;
[20]Institute of Child Health, University College London, 30 Guilford St, London WC1N 1EH, UK;
[21]University of Aberdeen, Institute of Medical Sciences, Foresterhill, Aberdeen, AB25 2ZD, UK;
[22]Department of Psychiatry, Division of Neuroscience, Birmingham University, Birmingham, B15 2QZ, UK;
[23]Department of Psychological Medicine, Henry Wellcome Building, School of Medicine, Cardiff Univeristy, Heath Park, Cardiff CF14 4XN, UK;
[24]SGDP, The Institute of Psychiatry, King's College London, De Crespigny Park Denmark Hill London SE5 8AF, UK;
[25]School of Neurology, Neurobiology and Psychiatry, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP, UK;

Coronary Artery Disease (Leeds): Stephen G Ball[26], Anthony J Balmforth[26], Jennifer H Barrett[26], Timothy D Bishop[26], Mark M Iles[26], Azhar Maqbool[26], Nadira Yuldasheva[26], Alistair S Hall[26]; **(Leicester):** Peter S Braund[10], Paul R Burton[1], Richard J Dixon[10], Massimo Mangino[10], Suzanne Stevens[10], Martin D Tobin[1], John R Thompson[1], Nilesh J Samani[10]

Crohn's Disease (Cambridge): Francesca Bredin[27], Mark Tremelling[27], Miles Parkes[27]; **(Edinburgh):** Hazel Drummond[28], Charles W Lees[28], Elaine R Nimmo[28], Jack Satsangi[28]; **(London):** Sheila A Fisher[29], Alastair Forbes[30], Cathryn M Lewis[29], Clive M Onnie[29], Natalie J Prescott[29], Jeremy Sanderson[31], Christopher G Matthew[29]; **(Newcastle):** Jamie Barbour[32], M Khalid Mohiuddin[32], Catherine E Todhunter[32], John C Mansfield[32]; **(Oxford):** Tariq Ahmad[33], Fraser R Cummings[33], Derek P Jewell[33]

Hypertension (Aberdeen): John Webster[34]; **(Cambridge):** Morris J Brown[35], David G Clayton[2]; **(Evry, France):** Mark G Lathrop[36]; **(Glasgow):** John Connell[37], Anna Dominiczak[37]; **(Leicester):** Nilesh J Samani[10]; **(London):** Carolina A Braga Marcano[38], Beverley Burke[38], Richard Dobson[38], Johannie Gungadoo[38], Kate L Lee[38], Patricia B Munroe[38], Stephen J Newhouse[38], Abiodun Onipinla[38], Chris Wallace[38], Mingzhan Xue[38], Mark Caulfield[38]; **(Oxford):** Martin Farrall[39]

Rheumatoid Arthritis: Anne Barton[40], The Biologics in RA Genetics and Genomics Study Syndicate (BRAGGS) Steering Committee*, Ian N Bruce[40], Hannah Donovan[40], Steve Eyre[40], Paul D Gilbert[40], Samantha L Hilder[40], Anne M Hinks[40], Sally L John[40], Catherine Potter[40], Alan J Silman[40], Deborah PM Symmons[40], Wendy Thomson[40], Jane Worthington[40]

Type 1 Diabetes: David G Clayton[2], David B Dunger[2,41], Sarah Nutland[2], Helen E Stevens[2], Neil M Walker[2], Barry Widmer[2,41], John A Todd[2]

Type 2 Diabetes (Exeter): Timothy M Frayling[42,43], Rachel M Freathy[42,43], Hana Lango[42,43], John R B Perry[42,43], Beverley M Shields[43], Michael N Weedon [42,43], Andrew T Hattersley[42,43]; **(London):** Graham A Hitman[44]; **(Newcastle):** Mark Walker[45];

[26]LIGHT and LIMM Research Institutes, Faculty of Medicine and Health, University of Leeds, Leeds, LS1 3EX, UK;
[27]IBD Research Group, Addenbrooke's Hospital, University of Cambridge, Cambridge, CB2 2QQ, UK;
[28]Gastrointestinal Unit, School of Molecular and Clinical Medicine, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU UK;
[29]Department of Medical & Molecular Genetics, King's College London School of Medicine, 8th Floor Guy's Hospital, London, SE1 9RT, UK;
[30]Institute for Digestive Diseases, University College London Hospitals Trust, London NW1 2BU, UK;
[31]Department of Gastroenterology, Guy's and St Thomas' NHS Foundation Trust, London, SE1 7EH, UK;
[32]Department of Gastroenterology & Hepatology, University of Newcastle upon Tyne, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, UK;
[33]Gastroenterology Unit, Radcliffe Infirmary, University of Oxford, Oxford, OX2 6HE, UK;
[34]Medicine and Therapeutics, Aberdeen Royal Infirmary, Foresterhill, Aberdeen, Grampian AB9 2ZB, UK;
[35]Clinical Pharmacology Unit and the Diabetes and Inflammation Laboratory, University of Cambridge, Addenbrookes Hospital, Hills Road, Cambridge CB2 2QQ, UK;
[36]Centre National de Genotypage, 2 Rue Gaston Cremieux, Evry, Paris 91057;
[37]BHF Glasgow Cardiovascular Research Centre, University of 28 Glasgow, 126 University Place, Glasgow, G12 8TA, UK;
[38]Clinical Pharmacology and Barts and The London Genome Centre, William Harvey Research Institute, Barts and The London, Queen Mary's School of Medicine, Charterhouse Square, London EC1M 6BQ, UK;
[39]Cardiovascular Medicine, University of Oxford, Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7BN, UK;
[40]arc Epidemiology Research Unit, University of Manchester, Stopford Building, Oxford Rd, Manchester, M13 9PT, UK;
[41]Department of Paediatrics, University of Cambridge, Addenbrooke's Hospital, Cambridge, CB2 2QQ, UK;
[42]Genetics of Complex Traits, Institute of Biomedical and Clinical Science, Peninsula Medical School, Magdalen Road, Exeter EX1 2LU, UK;
[43]Diabetes Genetics, Institute of Biomedical and Clinical Science, Peninsula Medical School, Barrack Road, Exeter EX2 5DU UK;
[44]Centre for Diabetes and Metabolic Medicine, Barts and The London, Royal London Hospital, Whitechapel, London, E1 1BB , UK;

(Oxford): Kate S Elliott[3,7], Christopher J Groves[7], Cecilia M Lindgren[3,7], Nigel W Rayner[3,7], Nicolas J Timpson[3,46], Eleftheria Zeggini[3,7], Mark I McCarthy[3,7]

Tuberculosis (Gambia): Melanie Newport[47], Giorgio Sirugo[47]; **(Oxford):** Emily Lyons[3], Fredrik Vannberg[3], Adrian VS Hill[3]

Ankylosing Spondylitis: Linda A Bradbury[48], Claire Farrar[49], Jennifer J Pointon[49], Paul Wordsworth[49], Matthew A Brown[48,49]

Autoimmune Thyroid Disease: Jayne A Franklyn[50], Joanne M Heward[50], Matthew J Simmonds[50], Stephen CL Gough[50]

Breast Cancer: Sheila Seal[51], Breast Cancer Susceptibility Collaboration (UK)*, Michael R Stratton[51,52], Nazneen Rahman[51]

Multiple Sclerosis: Maria Ban[53], An Goris[53], Stephen J Sawcer[53], Alastair Compston[53]

Gambian Controls (Gambia): David Conway[47], Muminatou Jallow[47], Melanie Newport[47], Giorgio Sirugo[47]; **(Oxford):** Kirk A Rockett[3], Dominic P Kwiatkowski[3,5]

DNA, Genotyping, Data QC and Informatics (Wellcome Trust Sanger Institute, Hinxton): Claire Bryan[5], Suzannah J Bumpstead[5], Amy Chaney[5], Kate Downes[2,5], Jilur Ghori[5], Rhian Gwilliam[5], Sarah E Hunt[5], Michael Inouye[5], Andrew Keniry[5], Emma King[5], Ralph McGinnis[5], Simon Potter[5], Rathi Ravindrarajah[5], Pamela Whittaker[5], David Withers[5], Panos Deloukas[5]; **(Cambridge):** Hin-Tak Leung[2], Sarah Nutland[2], Helen E Stevens[2], Neil M Walker[2], John A Todd[2]

Statistics (Cambridge): Doug Easton[12], David G Clayton[2]; **(Leicester):** Paul R Burton[1], Martin D Tobin[1]; **(Oxford):** Jeffrey C Barrett[3], David M Evans[3], Andrew P Morris[3], Lon R Cardon[3,55]; **(Oxford):** Niall J Cardin[11], Dan Davison[11], Teresa Ferreira[11], Joanne Pereira-Gale[11], Ingeleif B Hallgrimsdóttir[11], Bryan N Howie[11], Jonathan L Marchini[11], Chris CA Spencer[11], Zhan Su[11], Yik Ying Teo[3,11], Damjan Vukcevic[11], Peter Donnelly[11]

PIs: David Bentley[5,54], Matthew A Brown[48,49], Lon R Cardon[3,55], Mark Caulfield[38], David G Clayton[2], Alastair Compston[53], Nick Craddock[23], Panos Deloukas[5], Peter Donnelly[11], Martin Farrall[39], Stephen CL Gough[50], Alistair S Hall[26], Andrew T Hattersley[42,43], Adrian VS Hill[3], Dominic P Kwiatkowski[3,5], Christopher G Matthew[29], Mark I McCarthy[3,7], Willem H Ouwehand[8,9], Miles Parkes[27], Marcus Pembrey[18,20], Nazneen Rahman[51], Nilesh J Samani[10], Michael R Stratton[51,52], John A Todd[2], Jane Worthington[40]

[45]Diabetes Research Group, School of Clinical Medical Sciences, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4HH, UK;
[46]The MRC Centre for Causal Analyses in Translational Epidemiology, Bristol University, Canynge Hall, Whiteladies Rd, Bristol BS2 8PR, UK;
[47]MRC Laboratories, Fajara, The Gambia;
[48]Diamantina Institute for Cancer, Immunology and Metabolic Medicine, Princess Alexandra Hospital, University of Queensland, Woolloongabba, Qld 4102, Australia;
[49]Botnar Research Centre, University of Oxford, Headington, Oxford OX3 7BN, UK;
[50]Department of Medicine, Division of Medical Sciences, Institute of Biomedical Research, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK;
[51]Section of Cancer Genetics, Institute of Cancer Research, 15 Cotswold Road, Sutton, SM2 5NG, UK;
[52]Cancer Genome Project, The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK;
[53]Department of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK;
[54]PRESENT ADDRESS: Illumina Cambridge, Chesterford Research Park, Little Chesterford, NR Saffron Walden, Essex, CB10 1XL, UK;

AITD Replication Group: Sarah L Mitchell[50], Paul R Newby[50], Oliver J Brand[50], Jackie Carr-Smith[50], Simon HS Pearce[50] and Stephen CL Gough[50]

[1]Genetic Epidemiology Group, Department of Health Sciences, University of Leicester, Adrian Building, University Road, Leicester, LE1 7RH, UK;
[2]Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory, Department of Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge, Wellcome Trust/MRC Building, Cambridge, CB2 0XY, UK;
[3]Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK;
[4]Department of Psychological Medicine, Henry Welcome Building, School of Medicine, Cardiff University, Heath Park, Cardiff CF14 4XN, UK;
[5]The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK;
[6]The Wellcome Trust, Gibbs Building, 215 Euston Road, London NW1 2BE, UK;
[7]Oxford Centre for Diabetes, Endocrinology and Medicine, University of Oxford, Churchill Hospital, Oxford, OX3 7LJ, UK;
[8]Department of Haematology, University of Cambridge, Long Road, Cambridge, CB2 2PT, UK;
[9]National Health Service Blood and Transplant, Cambridge Centre, Long Road, Cambridge, CB2 2PT, UK;
[10]Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK;
[11]Department of Statistics, University of Oxford, 1 South Parks Road, Oxford OX1 3TG, UK;
[12]Cancer Research UK Genetic Epidemiology Unit, Strangeways Research Laboratory, Worts Causeway, Cambridge CB1 8RN, UK;
[13]National Health Service Blood and Transplant, Sheffield Centre, Longley Lane, Sheffield S5 7JN, UK;
[14]National Health Service Blood and Transplant, Brentwood Centre, Crescent Drive, Brentwood, CM15 8DP, UK;
[15]The Welsh Blood Service, Ely Valley Road, Talbot Green, Pontyclun, CF72 9WB, UK;
[16]The Scottish National Blood Transfusion Service, Ellen's Glen Road, Edinburgh, EH17 7QT, UK;
[17]National Health Service Blood and Transplant, Southampton centre, Coxford Road, Southampton, SO16 5AF, UK;
[18]Avon Longitudinal Study of Parents and Children, University of Bristol, 24 Tyndall Avenue, Bristol, BS8 1TQ, UK;
[19]Division of Community Health Services, St George's University of London, Crammer Terrace, London SW17 0RE, UK;
[20]Institute of Child Health, University College London, 30 Guilford St, London WC1N 1EH, UK;
[21]University of Aberdeen, Institute of Medical Sciences, Foresterhill, Aberdeen, AB25 2ZD, UK;
[22]Department of Psychiatry, Division of Neuroscience, Birmingham University, Birmingham, B15 2QZ, UK;
[23]Department of Psychological Medicine, Henry Wellcome Building, School of Medicine, Cardiff Univeristy, Heath Park, Cardiff CF14 4XN, UK;
[24]SGDP, The Institute of Psychiatry, King's College London, De Crespigny Park Denmark Hill London SE5 8AF, UK;
[25]School of Neurology, Neurobiology and Psychiatry, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP, UK;

[26]LIGHT and LIMM Research Institutes, Faculty of Medicine and Health, University of Leeds, Leeds, LS1 3EX, UK;
[27]IBD Research Group, Addenbrooke's Hospital, University of Cambridge, Cambridge, CB2 2QQ, UK;
[28]Gastrointestinal Unit, School of Molecular and Clinical Medicine, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU UK;
[29]Department of Medical & Molecular Genetics, King's College London School of Medicine, 8th Floor Guy's Hospital, London, SE1 9RT, UK;
[30]Institute for Digestive Diseases, University College London Hospitals Trust, London NW1 2BU, UK;
[31]Department of Gastroenterology, Guy's and St Thomas' NHS Foundation Trust, London, SE1 7EH, UK;
[32]Department of Gastroenterology & Hepatology, University of Newcastle upon Tyne, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, UK;
[33]Gastroenterology Unit, Radcliffe Infirmary, University of Oxford, Oxford, OX2 6HE, UK;
[34]Medicine and Therapeutics, Aberdeen Royal Infirmary, Foresterhill, Aberdeen, Grampian AB9 2ZB, UK;
[35]Clinical Pharmacology Unit and the Diabetes and Inflammation Laboratory, University of Cambridge, Addenbrookes Hospital, Hills Road, Cambridge CB2 2QQ, UK;
[36]Centre National de Genotypage, 2 Rue Gaston Cremieux, Evry, Paris 91057;
[37]BHF Glasgow Cardiovascular Research Centre, University of 28 Glasgow, 126 University Place, Glasgow, G12 8TA, UK;
[38]Clinical Pharmacology and Barts and The London Genome Centre, William Harvey Research Institute, Barts and The London, Queen Mary's School of Medicine, Charterhouse Square, London EC1M 6BQ, UK;
[39]Cardiovascular Medicine, University of Oxford, Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7BN, UK;
[40]arc Epidemiology Research Unit, University of Manchester, Stopford Building, Oxford Rd, Manchester, M13 9PT, UK;
[41]Department of Paediatrics, University of Cambridge, Addenbrooke's Hospital, Cambridge, CB2 2QQ, UK;
[42]Genetics of Complex Traits, Institute of Biomedical and Clinical Science, Peninsula Medical School, Magdalen Road, Exeter EX1 2LU, UK;
[43]Diabetes Genetics, Institute of Biomedical and Clinical Science, Peninsula Medical School, Barrack Road, Exeter EX2 5DU UK;
[44]Centre for Diabetes and Metabolic Medicine, Barts and The London, Royal London Hospital, Whitechapel, London, E1 1BB , UK;
[45]Diabetes Research Group, School of Clinical Medical Sciences, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4HH, UK;
[46]The MRC Centre for Causal Analyses in Translational Epidemiology, Bristol University, Canynge Hall, Whiteladies Rd, Bristol BS2 8PR, UK;
[47]MRC Laboratories, Fajara, The Gambia;
[48]Diamantina Institute for Cancer, Immunology and Metabolic Medicine, Princess Alexandra Hospital, University of Queensland, Woolloongabba, Qld 4102, Australia;
[49]Botnar Research Centre, University of Oxford, Headington, Oxford OX3 7BN, UK;
[50]Department of Medicine, Division of Medical Sciences, Institute of Biomedical Research, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK;
[51]Section of Cancer Genetics, Institute of Cancer Research, 15 Cotswold Road, Sutton, SM2 5NG, UK;
[52]Cancer Genome Project, The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK;

[53]Department of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK;
[54]PRESENT ADDRESS: Illumina Cambridge, Chesterford Research Park, Little Chesterford, NR Saffron Walden, Essex, CB10 1XL, UK;
[55]PRESENT ADDRESS: Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, Seattle, Washington 98109 USA.

+: The Australo-Anglo-American Spondylitis Consortium (TASC)

John D. Reveille[1], Xiaodong Zhou,1, Linda A Bradbury[2], Anne-Marie Sims[2], Alison Dowling[2], Jacqueline Taylor[2], Tracy Doan[2], Lon R. Cardon[3,55], John C Davis[4], Jennifer J Pointon[5], Laurie Savage[6], Michael M Ward[7], Thomas L Learch[8], Michael H Weisman[9], Paul Wordsworth[5], Matthew A Brown[2,5]

[1]Rheumatology and Clinical Immunogenetics, University of Texas-Houston Medical School, Houston, United States;
[2]Diamantina Institute for Cancer, Immunology and Metabolic Medicine, University of Queensland, Brisbane, Australia;
[3]Statistical Genetics, Wellcome Trust Centre for Human Genetics, Oxford, United Kingdom;
[4]Rheumatology, University of California, San Francisco, San Francisco, United States;
[5]Botnar Research Centre, University of Oxford, Oxford, United Kingdom;
[6]The Spondylitis Association of America, Sherman, Oaks, CA;
[7]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, United States;
[8]Department of Radiology, Cedars-Sinai Medical Centre, Los Angeles, United States;
[9]Department of Medicine/Rheumatology, Cedars-Sinai Medical Centre, Los Angeles, United States.

References

1. Rioux JD, et al. Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. Nat Genet. 2007; 39:596–604. [PubMed: 17435756]
2. Sladek R, et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. Nature. 2007; 445:881–5. [PubMed: 17293876]
3. Easton DF, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature. 2007; 447:1087–93. [PubMed: 17529967]
4. Libioulle C, et al. Novel Crohn disease locus identified by genome-wide association maps to a gene desert on 5p13.1 and modulates expression of PTGER4. PLoS Genet. 2007; 3:e58. [PubMed: 17447842]
5. Zanke BW, et al. Genome-wide association scan identifies a colorectal cancer susceptibility locus on chromosome 8q24. Nat Genet. 2007; 39:989–994. [PubMed: 17618283]
6. Haiman CA, et al. Multiple regions within 8q24 independently affect risk for prostate cancer. Nat Genet. 2007; 39:638–44. [PubMed: 17401364]

[1]Rheumatology and Clinical Immunogenetics, University of Texas-Houston Medical School, Houston, United States;
[2]Diamantina Institute for Cancer, Immunology and Metabolic Medicine, University of Queensland, Brisbane, Australia;
[3]Statistical Genetics, Wellcome Trust Centre for Human Genetics, Oxford, United Kingdom;
[4]Rheumatology, University of California, San Francisco, San Francisco, United States;
[5]Botnar Research Centre, University of Oxford, Oxford, United Kingdom;
[6]The Spondylitis Association of America, Sherman, Oaks, CA;
[7]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, United States;
[8]Department of Radiology, Cedars-Sinai Medical Centre, Los Angeles, United States;
[9]Department of Medicine/Rheumatology, Cedars-Sinai Medical Centre, Los Angeles, United States.

Europe PMC Funders Author Manuscripts

7. Gudmundsson J, et al. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. Nat Genet. 2007; 39:977–83. [PubMed: 17603485]
8. Moffatt MF, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. Nature. 2007; 448:470–3. [PubMed: 17611496]
9. Zeggini E, et al. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. Science. 2007; 316:1336–41. [PubMed: 17463249]
10. Scott LJ, et al. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. Science. 2007; 316:1341–5. [PubMed: 17463248]
11. Saxena R, et al. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science. 2007; 316:1331–6. [PubMed: 17463246]
12. WTCCC. Genome-wide association studies of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007; 447:661–683. [PubMed: 17554300]
13. Hampe J, et al. A genome-wide association scan of nonsynonymous SNPs identifies a susceptibility variant for Crohn disease in ATG16L1. Nat Genet. 2007; 39:207–211. [PubMed: 17200669]
14. Jorgenson E, Witte JS. Coverage and power in genomewide association studies. Am J Hum Genet. 2006; 78:884–8. [PubMed: 16642443]
15. Smyth DJ, et al. A genome-wide association study of nonsynonymous SNPs identifies a type 1 diabetes locus in the interferon-induced helicase (IFIH1) region. Nat Genet. 2006; 38:617–9. [PubMed: 16699517]
16. Miretti MM, et al. A high-resolution linkage-disequilibrium map of the human major histocompatibility complex and first generation of tag single-nucleotide polymorphisms. Am J Hum Genet. 2005; 76:634–46. [PubMed: 15747258]
17. Clayton DG, et al. Population structure, differential bias and genomic control in a large-scale, case-control association study. Nat Genet. 2005; 37:1243–6. [PubMed: 16228001]
18. Sims AM, et al. Non-B27 MHC associations of ankylosing spondylitis. Genes Immun. 2007; 8:115–23. [PubMed: 17167495]
19. McGinnis R, Shifman S, Darvasi A. Power and efficiency of the TDT and case-control design for association scans. Behav Genet. 2002; 32:135–44. [PubMed: 12036111]
20. Devlin B, Roeder K. Genomic control for association studies. Biometrics. 1999; 55:997–1004. [PubMed: 11315092]
21. Thomas DC, Clayton DG. Betting odds and genetic associations. J Natl Cancer Inst. 2004; 96:421–3. [PubMed: 15026459]
22. Jiang HR, et al. Sialoadhesin promotes the inflammatory response in experimental autoimmune uveoretinitis. J Immunol. 2006; 177:2258–64. [PubMed: 16887986]
23. Dechairo BM, et al. Association of the TSHR gene with Graves' disease: the first disease specific locus. Eur J Hum Genet. 2005; 13:1223–30. [PubMed: 16106256]
24. Hiratani H, et al. Multiple SNPs in intron 7 of thyrotropin receptor are associated with Graves' disease. J Clin Endocrinol Metab. 2005; 90:2898–903. [PubMed: 15741259]
25. Miettinen O. Proportion of disease caused or prevented by a given exposure, trait or intervention. Am J Epidemiol. 1974; 99:325–332. [PubMed: 4825599]
26. Duerr RH, et al. A Genome-Wide Association Study Identifies IL23R as an Inflammatory Bowel Disease Gene. Science. 2006
27. Tremelling M, et al. IL23R variation determines susceptibility but not disease phenotype in inflammatory bowel disease. Gastroenterology. 2007; 132:1657–64. [PubMed: 17484863]
28. Cargill M, et al. A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. Am J Hum Genet. 2007; 80:273–90. [PubMed: 17236132]
29. Simmonds MJ, et al. Contribution of single nucleotide polymorphisms within FCRL3 and MAP3K7IP2 to the pathogenesis of Graves' disease. J Clin Endocrinol Metab. 2006; 91:1056–61. [PubMed: 16384851]

30. Kochi Y, et al. A functional variant in FCRL3, encoding Fc receptor-like 3, is associated with rheumatoid arthritis and several autoimmunities. Nat Genet. 2005; 37:478–85. [PubMed: 15838509]
31. Capon F, et al. Fine mapping of the PSORS4 psoriasis susceptibility region on chromosome 1q21. J Invest Dermatol. 2001; 116:728–30. [PubMed: 11348461]
32. Dai KZ, et al. The T cell regulator gene SH2D2A contributes to the genetic susceptibility of multiple sclerosis. Genes Immun. 2001; 2:263–8. [PubMed: 11528519]
33. Chang SC, Momburg F, Bhutani N, Goldberg AL. The ER aminopeptidase, ERAP1, trims precursors to lengths of MHC class I peptides by a “molecular ruler” mechanism. Proc Natl Acad Sci U S A. 2005; 102:17107–12. [PubMed: 16286653]
34. Saveanu L, et al. Concerted peptide trimming by human ERAP1 and ERAP2 aminopeptidase complexes in the endoplasmic reticulum. Nat Immunol. 2005; 6:689–97. [PubMed: 15908954]
35. Brown MA, et al. HLA class I associations of ankylosing spondylitis in the white population in the United Kingdom. Ann Rheum Dis. 1996; 55:268–70. [PubMed: 8733445]
36. Cui X, Rouhani FN, Hawari F, Levine SJ. Shedding of the type II IL-1 decoy receptor requires a multifunctional aminopeptidase, aminopeptidase regulator of TNF receptor type 1 shedding. J Immunol. 2003; 171:6814–9. [PubMed: 14662887]
37. Cui X, Rouhani FN, Hawari F, Levine SJ. An aminopeptidase, ARTS-1, is required for interleukin-6 receptor shedding. J Biol Chem. 2003; 278:28677–85. [PubMed: 12748171]
38. Cui X, et al. Identification of ARTS-1 as a novel TNFR1-binding protein that promotes TNFR1 ectodomain shedding. J Clin Invest. 2002; 110:515–26. [PubMed: 12189246]
39. Cua DJ, et al. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. Nature. 2003; 421:744–8. [PubMed: 12610626]
40. Murphy CA, et al. Divergent pro- and antiinflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation. J Exp Med. 2003; 198:1951–7. [PubMed: 14662908]
41. Hue S, et al. Interleukin-23 drives innate and T cell-mediated intestinal inflammation. J Exp Med. 2006; 203:2473–83. [PubMed: 17030949]
42. Mannon PJ, et al. Anti-interleukin-12 antibody for active Crohn’s disease. N Engl J Med. 2004; 351:2069–79. [PubMed: 15537905]
43. Hunter DJ, et al. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. Nat Genet. 2007; 39:870–4. [PubMed: 17529973]
44. Cohen JC, et al. Multiple rare alleles contribute to low plasma levels of HDL cholesterol. Science. 2004; 305:869–72. [PubMed: 15297675]
45. A haplotype map of the human genome. Nature. 2005; 437:1299–320. [PubMed: 16255080]
46. Wigginton JE, Cutler DJ, Abecasis GR. A note on exact tests of Hardy-Weinberg equilibrium. Am J Hum Genet. 2005; 76:887–93. [PubMed: 15789306]
47. Armitage P. Test for linear trend in proportions and frequencies. Biometrics. 1955; 11:375–386.
48. Purcell S, et al. PLINK: A Tool Set for Whole-Genome Association and Population-Based Linkage Analyses. Am J Hum Genet. 2007; 81:559–75. [PubMed: 17701901]
49. Purcell S, Daly MJ, Sham PC. WHAP: haplotype-based association analysis. Bioinformatics. 2007; 23:255–6. [PubMed: 17118959]
50. Marchini J, Cardon LR, Phillips MS, Donnelly P. The effects of human population structure on large genetic association studies. Nat Genet. 2004

Europe PMC Funders Author Manuscripts

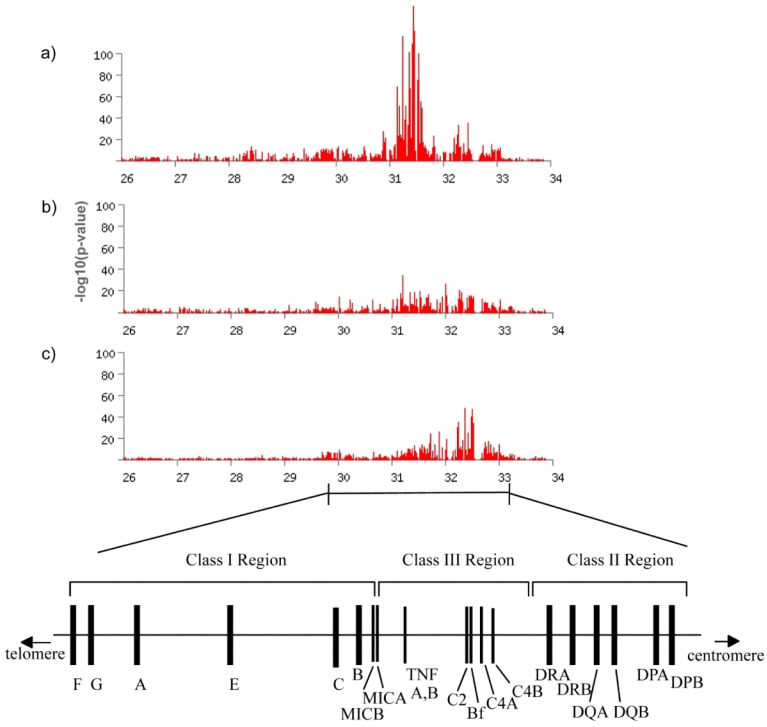

Figure 1.

Minus $\log_{10}$ p values for the Armitage test of trend for MHC association with Ankylosing Spondylitis (top panel), Auto-Immune Thyroid Disease (middle panel), and Multiple Sclerosis (bottom panel). Note in particular how evidence for association extends along very long regions of the MHC, reflecting statistical power to detect association even when linkage disequilibrium amongst SNPs is relatively low and/or the possibility of multiple disease-predisposing loci.

Europe PMC Funders Author Manuscripts

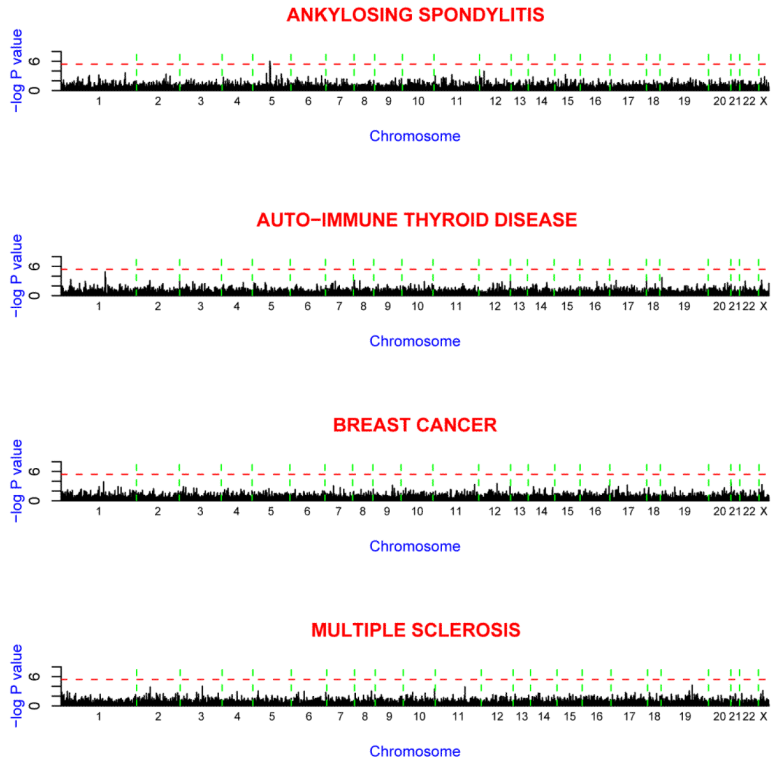

Figure 2.

Minus $\log_{10}$ p values for the Armitage test of trend for genome-wide association scans of ankylosing spondylitis, auto-immune thyroid disease, breast cancer and multiple sclerosis. The spacing between SNPs on the plot is uniform and does not reflect distances between the SNPs. The vertical dashed lines reflect chromosomal boundaries. The horizontal dashed lines display the cutoff of $p = 10^{-6}$. Note that SNPs within the MHC are not included in this diagram.

Europe PMC Funders Author Manuscripts

Table 1

Number of individuals and SNPs tested in each cohort

	Cohort				
	AS	**AITD**	**BC**	**MS**	**58C**
Males	610	138	0	271	732
Females	312	762	1004	704	734
Number of SNPs genotyped	15,436	15,436	15,436	15,436	15,436
SNPs with Low GC score	783	816	771	802	796
SNPs with Low Genotyping	133	206	124	218	186
Monomorphic SNPs	1,842	1,829	1,854	1,810	1,687
SNPs with HW $p < 10^{-7}$ *	129	74	104	97	132
Differences in missing rate $p < 10^{-4}$	51	101	172	309	n/a
“Manual” Exclusions	33	33	33	33	33
Total Number of SNPs tested	12,701	12,572	12,577	12,374	

* Only SNPs with HW $p < 10^{-7}$ in the 58C control group were excluded from analyses

Nat Genet. Author manuscript; available in PMC 2009 May 11.

Europe PMC Funders Author Manuscripts

Table 2

Estimates of λ for Single and Combined Cohorts

		λ
Single Cohort		
	AS cases vs 1958	1.07
	AITD cases vs 1958	1.12
	BC cases vs 1958	1.13
	MS cases vs 1958	1.12
Mixed Cohorts		
	AS cases vs All Others	1.03
	AITD cases vs All Others	1.05
	BC cases vs All Others	1.04
	MS cases vs All Others	1.06
	IMMUNE cases vs BC and 58C	1.04

Europe PMC Funders Author Manuscripts

Table 3

nsSNPs outside the MHC which meet a point-wise significance level of $p < 10^{-3}$ for the Cochran-Armitage test for trend

Disease	SNP	Chromosome	Position (bp)	MAF	OR	χ^2	p value	Gene
AS								
	rs696698	1	74777462	.04	1.84	11.13	8.5×10^{-4}	C1orf173
	rs10494217	1	119181230	.17	0.77	11.62	6.5×10^{-4}	TBX15
	rs2294851	1	206966279	.13	0.73	13.55	2.3×10^{-4}	HHAT
	rs8192556	2	182368504	.01	0.45	12.24	4.7×10^{-4}	NEUROD1
	rs16876657	5	78645930	.02	3.10	13.05	3.0×10^{-4}	JMY
	rs27044	5	96144608	.34	1.40	23.90	1.0×10^{-6}	ARTS-1
	rs17482078	5	96144622	.17	0.76	13.55	2.3×10^{-4}	ARTS-1
	rs10050860	5	96147966	.18	0.75	14.87	1.1×10^{-4}	ARTS-1
	rs30187	5	96150086	.40	1.33	21.82	3.0×10^{-6}	ARTS-1
	rs2287987	5	96155291	.18	0.75	14.31	1.6×10^{-4}	ARTS-1
	rs2303138	5	96376466	.10	1.58	19.41	1.1×10^{-5}	LNPEP
	rs11750814	5	137528564	.16	0.77	10.99	9.1×10^{-4}	BRD8
	rs11959820	5	149192703	.02	0.49	12.41	4.3×10^{-4}	PPARGC1B
	rs907609	11	1813846	.13	0.76	10.91	9.5×10^{-4}	SYT8
	rs3740691	11	47144987	.29	0.80	11.86	5.7×10^{-4}	ZNF289
	rs11062385	12	297836	.24	0.79	11.82	5.9×10^{-4}	JARID1A
	rs7302230	12	7179699	.08	1.57	14.97	1.1×10^{-4}	CLSTN3
AITD								
	rs10916769	1	20408244	.17	0.76	12.10	5.0×10^{-4}	FLJ32784
	rs6427384	1	154321955	.18	1.43	18.97	1.3×10^{-5}	FCRL5
	rs2012199	1	154322098	.17	1.35	13.18	2.8×10^{-4}	FCRL5
	rs6679793	1	154327170	.22	1.33	14.69	1.3×10^{-4}	FCRL5
	rs7522061	1	154481463	.47	1.25	13.78	2.1×10^{-4}	FCRL3
	rs1047911	2	74611433	.15	1.34	11.24	8.0×10^{-4}	MRPL53
	rs7578199	2	241912838	.26	1.26	11.53	6.9×10^{-4}	HDLBP
	rs3748140	8	9036429	.00	0.28	11.44	7.2×10^{-4}	PPP1R3B
	rs1048101	8	26683945	.42	0.82	10.98	9.2×10^{-4}	ADRA1A

Disease	SNP	Chromosome	Position (bp)	MAF	OR	χ^2	p value	Gene
	rs7975069	12	132389146	.30	0.80	12.06	5.2×10^{-4}	ZNF268
	rs2271233	17	6644845	.07	0.94	11.32	7.7×10^{-4}	TEKT1
	rs2856966	18	897710	.19	0.76	14.00	1.8×10^{-4}	ADCYAP1
	rs7250822	19	2206311	.04	1.97	13.83	2.0×10^{-4}	AMH
	rs2230018	23	44685331	.14	1.41	11.55	6.8×10^{-4}	UTX
BC								
	rs4255378	1	151919300	.48	1.25	14.70	1.3×10^{-4}	MUC1
	rs2107732	7	44851218	.10	1.40	10.96	9.3×10^{-4}	CCM2
	rs4986790	9	117554856	.07	1.54	11.46	7.1×10^{-4}	TLR4
	rs2285374	11	118457383	.38	0.82	12.25	4.7×10^{-4}	VPS11
	rs7313899	12	54231386	.03	2.10	13.02	3.1×10^{-4}	OR6C4
	rs2879097	17	34143085	.20	0.78	11.73	6.1×10^{-4}	MEL18
	rs2822558	21	14593715	.13	0.73	13.87	2.0×10^{-4}	ABCC13
	rs2230018	23	44685331	.14	1.40	12.14	4.9×10^{-4}	UTX
MS								
	rs17009792	2	74400978	.02	0.44	14.41	1.5×10^{-4}	SLC4A5
	rs1132200	3	120633526	.15	0.73	15.22	9.6×10^{-5}	FLJ10902
	rs6897932	5	35910332	.23	0.80	11.04	8.9×10^{-4}	IL7R
	rs6470147	8	124517985	.36	1.23	10.92	9.5×10^{-4}	FLJ10204
	rs3818511	10	134309378	.24	1.28	12.84	3.4×10^{-4}	INPP5A
	rs11574422	11	67970565	.02	2.82	14.64	1.3×10^{-4}	LRP5
	rs388706	19	49110533	.48	1.22	11.19	8.2×10^{-4}	ZNF45
	rs1800437	19	50873232	.17	0.74	16.11	6.0×10^{-5}	GIPR
	rs2281868	23	69451484	.50	1.26	11.38	7.4×10^{-4}	SAP102

Europe PMC Funders Author Manuscripts

Table 4

Ankylosing Spondylitis Replication Results

Gene	SNP	UK Cases				US Cases				All Cases			
		Case MAF	Control MAF	OR	p val	Case MAF	Control MAF	OR	p val	Case MAF	Control MAF	OR	p val
ARTS1	rs27044	0.34	0.27	1.40	1.0×10^{-6}	-	-	-	-	-	-	-	-
ARTS1	rs17482078	0.17	0.22	0.76	2.3×10^{-4}	0.15	0.21	0.65	5.1×10^{-5}	0.16	0.22	0.70	1.2×10^{-8}
ARTS1	rs10050860	0.18	0.23	0.75	1.2×10^{-4}	0.15	0.22	0.66	8.8×10^{-5}	0.17	0.22	0.71	7.6×10^{-9}
ARTS1	rs30187	0.40	0.33	1.33	3.0×10^{-6}	0.41	0.35	1.30	0.00047	0.41	0.34	1.40	3.4×10-10
ARTS1	rs2287987	0.18	0.22	0.75	1.6×10^{-4}	0.15	0.21	0.66	8.4×10^{-5}	0.17	0.22	0.71	1.0×10^{-8}
LNPEP	rs2303138	0.10	0.07	1.58	1.1×10^{-5}	0.11	0.09	1.40	0.018	0.11	0.07	1.48	1.1×10^{-6}
CLSTN3	rs7302230	0.08	0.05	1.57	1.1×10^{-4}	0.06	0.05	1.10	0.56	0.07	0.05	1.30	0.0039
IL23R	rs11209026	0.04	0.06	0.63	0.0017	0.038	0.06	0.63	0.014	0.04	0.06	0.63	4.0×10^{-6}
IL23R	rs1004819	0.35	0.30	1.20	0.0013	0.35	0.30	1.30	0.0045	0.35	0.30	1.20	1.1×10^{-5}
IL23R	rs10489629	0.43	0.45	0.90	0.062	0.39	0.47	0.72	4.2×10^{-5}	0.41	0.46	0.83	0.00011
IL23R	rs11465804	0.04	0.06	0.67	0.0019	0.049	0.06	0.68	0.04	0.04	0.06	0.68	0.0002
IL23R	rs1343151	0.30	0.34	0.85	0.0077	0.29	0.36	0.71	6.7×10^{-5}	0.30	0.34	0.80	1.0×10^{-5}
IL23R	rs10889677	0.36	0.31	1.20	0.00066	0.37	0.29	1.40	4.7×10^{-5}	0.36	0.31	1.30	1.3×10^{-6}
IL23R	rs11209032	0.38	0.32	1.30	2.0×10^{-6}	0.38	0.32	1.30	0.0013	0.38	0.32	1.30	7.5×10^{-9}
IL23R	rs1495965	0.49	0.44	1.20	0.0021	0.50	0.43	1.40	0.00019	0.49	0.44	1.20	3.1×10^{-6}

Europe PMC Funders Author Manuscripts

Table 5

Auto-immune Thyroid Disease Replication Results

Gene	SNP	Replication Cohort				Combined Cohort			
		Case MAF	Control MAF	OR	p val	Case MAF	Control MAF	OR	p val
FCRL3	rs3761959*	0.48	0.45	0.90	0.029	0.49	0.45	0.87	9.4×10^{-3}
FCRL3	rs11264794	0.42	0.46	1.10	0.079	0.42	0.46	1.12	0.013
FCRL3	rs11264793	0.27	0.24	0.87	0.020	0.26	0.24	0.90	0.044
FCRL3	rs11264798	0.44	0.49	1.21	4.0×10^{-3}	0.44	0.49	1.22	1.6×10^{-5}
FCRL3	rs10489678	0.19	0.20	1.07	0.30	0.20	0.20	1.04	0.43
FCRL3	rs6691569	0.28	0.28	1.03	0.60	0.29	0.29	1.00	0.93
FCRL3	rs2282284	0.062	0.058	0.92	0.013	0.062	0.058	0.93	0.47
FCRL5	rs6667109	0.17	0.15	0.91	0.18	0.18	0.15	0.85	7.7×10^{-2}

*This SNP tags the SNP rs7522061 which was flagged as associated with AITD in the WTCCC screen ($p = 2.1 \times 10^{-4}$)