Sharing information between related diseases using Bayesian joint fine mapping increases accuracy and identifies novel associations in six immune mediated diseases

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Abstract

Thousands of genetic variants have been associated with human disease risk, but linkage disequilibrium (LD) hinders fine-mapping the causal variants. We show that stepwise regression, and, to a lesser extent, stochastic search fine mapping can mis-identify as causal, SNPs which jointly tag distinct causal variants. Frequent sharing of causal variants between immune-mediated diseases (IMD) motivated us to develop a computationally efficient multinomial fine-mapping (MFM) approach that borrows information between diseases in a Bayesian framework. We show that MFM has greater accuracy than single disease analysis when shared causal variants exist, and negligible loss of precision otherwise. Applying MFM to data from six IMD revealed causal variants undetected in individual disease analysis, including in \( IL2RA \) where we confirm functional effects of multiple causal variants using allele-specific expression in sorted CD4\(^+\) T cells from genotype-selected individuals. MFM has the potential to increase fine-mapping resolution in related diseases enabling the identification of associated cellular and molecular phenotypes.
Introduction

The underlying genetic contribution to many complex diseases and traits has been investigated with great success by genome-wide association studies (GWAS). Various approaches have been developed to identify regions associated with individual diseases, and these have led to the detection of thousands of variants associated with a spectrum of diseases. In particular, much progress has been made in the genetics of immune mediated diseases (IMD), revealing a complex pattern of shared and overlapping genetic etiology\(^1,2\).

Fine mapping - the process of distinguishing causal genetic variants from their neighbours - is an essential step to enable the design of functional assays required to understand the mechanism by which the region impacts disease risk, but it is complicated by linkage disequilibrium (LD)\(^3\). The problem is often approached through stepwise regression\(^4\) which assumes that statistical inference of the best joint model (i.e. a model with multiple causal SNPs) can be derived by starting with the most significant SNP, then conditioning on this and adding the next most significant, continuing this conditioning until no conditionally significant SNPs remain. It has been noted that the SNP with the smallest p value need not be causal, especially if it is in LD with two causal SNPs.\(^5\) Alternative Bayesian fine mapping methods have been developed which use a stochastic search instead of stepwise search\(^6-8\). Stepwise and stochastic search results may disagree\(^8\) and although stochastic search generally demonstrates improved accuracy\(^9\) these techniques have not yet been widely adopted.

Here, we systematically compare stepwise and stochastic approaches by application to dense genotype data for six IMD. We aim to address, in particular, the frequency and causes of disagreement between stochastic and stepwise search results. Our results show that stochastic search solutions are more likely to be correct than stepwise search results when sample sizes are
large, but that they can face similar issues to stepwise searches when sample sizes are small. We also observe a striking sharing of causal variants between different IMD, consistent with previous reports\(^1,^2\), which motivates us to propose a novel Bayesian multinomial stochastic search method, in which multiple related diseases can be simultaneously fine mapped. This allows us to borrow information between diseases and achieve correct fine mapping solutions at smaller sample sizes than when considering individual diseases alone. We show that posterior probabilities under our proposed model can be decomposed into quantities directly available from single disease analyses, allowing it to be applied without excessive additional computational overhead.

**Results**

**Stochastic and stepwise search differences in 10% of regions**

We systematically applied stepwise and stochastic search fine mapping to dense genotyping data from ImmunoChip studies of six IMD: type 1 diabetes (T1D)\(^10\), multiple sclerosis (MS)\(^11\), autoimmune thyroid disease (ATD)\(^12\), celiac disease (CEL)\(^13\), juvenile idiopathic arthritis (JIA)\(^14\) and rheumatoid arthritis (RA)\(^15\) (sample sizes given in Supplementary Table 1) in 90 densely mapped regions with at least one associated disease (Supplementary Table 2), 204 disease-region-cohort combinations in total. Results are given in Supplementary Tables 3-4. For RA and CEL, we performed parallel analyses in UK-only and UK+international samples ("iRA" and "iCEL", respectively).

Note that, unlike stepwise search which produces a single best model, stochastic search results are a posterior probability distribution across typically thousands of potential causal variant models. To make these more interpretable, SNPs in high LD which meet the criteria of substitutability (see Methods) were grouped. The identification of SNP groups is a feature of stochastic search - generally, SNPs in a group have high LD and similar evidence for association, such that a single
candidate causal variant is not statistically distinguishable within the group. In general we prefer to consider posterior support for each SNP group ("gPP") when interpreting the stochastic search results.

In all regions, the model preferred by stochastic search either had equal or better Bayesian Information Criterion (BIC) and equal or larger number of variants compared to the model chosen by stepwise search (Supplementary Fig. 1). For 16 regions (18 disease-region pairs) the stepwise model was nested in that of stochastic search (treating SNPs in strong LD as equivalent; Supplementary Table 5). In six regions (6 disease-region pairs) there appeared to be two separate signals, both weak \(2 \times 10^{-10} < p < 4 \times 10^{-6}\) with stochastic search posterior support fairly evenly shared between the two SNP groups, and the SNP selected by stepwise search happened to fall in the group with slightly less posterior support (Table 1). In a further four regions (5 disease-region pairs) we found non-nested stochastic/stepwise mismatches, which could not be explained simply.

**Joint tagging of stochastic search models by stepwise SNPs**

We investigated these five mismatch cases further, both mathematically and using simulation, hypothesising that they may reflect cases where the SNP with smallest p value acts to tag both of two distinct causal variants\(^{16}\). We walk through these results using the example of ATD in a chromosome 10p region. Haplotype analysis, which estimates effects for all observed combinations of alleles across these three SNPs, illustrates how the minor allele of stepwise search-selected SNP rs706779 (group “J”) tends to be carried together with the minor alleles of stochastic search-selected SNPs rs61839660 (group “A”) and rs11594656 (group “C”) (Fig 1a).

Considering the haplotypes formed from rs706779/J, rs61839660/A and rs11594656/C, we see that while haplotypes carrying the rs706779:C allele in the presence of either rs61839660:T or rs11594656:A (haplotypes CTT or CCA) are protective for ATD, a haplotype carrying rs706779:C
in combination with rs61839660:C and rs11594656:T (CCT, frequency 13%) is indistinguishable from the common (susceptible) haplotype TCT (Fig. 1a, p=0.24).

First, simulations showed that if the J model were true, both stepwise and stochastic search would correctly identify it (Fig. 1b, Supplementary Table 6). In contrast, if the A+C model were true, stepwise got “stuck” on J, while stochastic search moved from selecting J at lower sample sizes, to A+C at higher sample sizes (Fig. 1b, Supplementary Table 7, further examples in other regions/diseases in Supplementary Tables 8-11). A small perturbation on the simulated effect sizes for A+C led both methods to select C or A+C directly, indicating that the potential for joint tagging was dependent on the combined effect sizes.

Second, we showed mathematically that there was a high probability of J having the smallest p value when A and C were causal only when A and C had similar odds ratios; and that our observed data fell within this region (Fig. 1c). Again, a similar pattern was seen at all other mismatch regions (Supplementary Fig. 2).
Figure 1: Evidence for joint tagging. a Haplotype analysis of SNPs selected by stepwise search and GUESSFM for ATD in region 10p-6030000-6220000. There are four common haplotypes. Three carry the minor allele at the J SNP rs706799, but only those that also carry minor allele at A or C show a significant effect on disease risk. b Comparison of stepwise and stochastic search applied to simulated data. Causal variants were simulated as follows: “J”: single causal variant J, OR=0.8; “A<C” causal variants A+C, odds ratios A:0.81, C:0.74; “A>C”: causal variants A+C, odds ratios A:0.74, C:0.8. The y axis shows the proportion of simulations in which the stepwise approach chose the indicated model (adding SNPs while p < 10^{-6}) or the average posterior probabilities for each model for the stochastic search approach. Sample size (x axis) is the number of cases and controls. c Assuming A and C are causal, this plot shows the probability that J has the smallest p value as a function of the effect sizes (log odds ratios) at A and C. The estimated effects for A and C from real data are shown by a point, and the simulations from b by “<” and “>” for A<C and A>C conditions, respectively.
Finally, we showed that the pattern of LD between three SNPs (two causal and a third tag), together with MAF (minor allele frequency) and effect sizes, determine whether a tag SNP has the smallest expected p value (Fig. 2a, Supplementary Note). At the extremes of this pattern, there is a non-zero probability that the tag model will be erroneously selected, even by a criterion such as BIC which penalizes the larger model (Supplementary Note). While we cannot identify how many cases of joint tagging may exist in our GWAS data because the causal variants are unknown, we can quantify what proportion of 3 SNP LD matrices match this pattern under an assumption of equal odds ratios at the causal variants. Doing so, we found that 20-40% of potential common causal variant pairs (MAF>5%) had a potential joint tag, though this was highly variable across regions (Fig 2b-c), although this must be considered an upper limit because effect sizes do not need to be equal across neighbouring causal variants.
Figure 2: Potential frequency of joint tagging. We consider the patterns of three-way LD between each possible trio of SNPs, nominating the first two as causal, and the third as a potential tag. a For each pair of potential causal SNPs, we can predict whether the third SNP is a tag according to the pairwise correlation between that SNP and the two potentially causal SNPs (r1, r2). In this example, the potentially causal SNPs have equal MAF, equal effect on disease risk (equal odds ratios, OR) and are uncorrelated. Then, if the third SNP is (A) uncorrelated with both, or (B, C) negatively correlated with one and positively with the other, we would not expect it to act as a tag. On the other hand, if it were (D, E) positively or negatively correlated with both causal variants, we would expect it to act as a joint tag. b shows the result of searching all possible SNP trios in UK ImmunoChip control data, and quantifying the proportion of trios that correspond to joint tagging in each region, assuming the causal variants have equal OR; the pattern is individually rare, consistently <5%. c shows the proportion of SNP pairs for which at least one potential tag exists, which can be substantial - about 40% overall.
Together, these results better characterize and quantify the potential frequency of joint tagging, in which a non-causal SNP carried on population haplotypes together with distinct causal SNPs with similar effects may have a smaller single SNP p value than either causal variant itself. This can cause stepwise search to get “stuck” on the tag, whereas stochastic search will find both causal variants, if the sample sizes are large enough. However, with smaller sample sizes, stochastic search may also choose the tag, because small sample sizes may not contain enough information to overcome the strong penalty that needs to be applied to more complex models to avoid overfitting. Thus, joint tagging may potentially affect many more cases than the simple comparison of stepwise and stochastic search results based on fixed sample sizes above identify.

Proposed method for multinomial fine mapping (MFM) of multiple diseases

We noticed a striking overlap between the fine mapping results for different diseases in these regions, with 20 of 30 regions with two or more associated diseases showing evidence of overlap (Supplementary Fig. 3), consistent with previous reports of shared genetic etiology between the diseases\(^2\) which inspired the creation of the ImmunoChip. This motivated us to exploit the sharing between diseases, by extending the stochastic search approach to jointly analyse multiple diseases, borrowing information between them, to help overcome these sample size limitations.

We use a multinomial logistic regression framework which is the natural extension of the binomial logistic model, in which each individual is assumed to belong to exactly one disease group or a pooled group of controls shared between diseases. This formally accounts for the sharing of controls between diseases in different studies.

We introduce the concept of “configurations” - sets of causal variant models for each disease, and we borrow information between the diseases by means of a prior which upweights configurations that share one or more causal variants between diseases by a factor \(\kappa\) (Fig. 3). Such a parameter
is also used in colocalization analysis, with values ranging from $100^{1,17}$ to $1000^{18}$. In the case of MFM, it may be easier to elicit a prior on the chance of any sharing in causal variants between a pair of diseases, and we show in the Supplementary Information how this value can be used to derive $\kappa$ for two or more diseases. In all our simulations and analyses, we chose $\kappa$ so that the prior on any pair of diseases sharing at least one causal variant in a region where they are both associated is $0.5^1$. 


Figure 3: Schematic diagram for Multinomial Fine-Mapping (MFM) method of multiple diseases with shared controls, where for simplicity only two diseases are shown. After selection of a sparsity prior parameterised by $\pi$, stochastic search is applied individually to each disease, as in standard analyses. Marginal results are combined in MFM, using an approximation to the multinomial Bayes factor (BF) and with information shared between diseases using a sharing prior which upweights joint models with shared causal variants by a factor $\kappa$. Memory constraints are dealt with by storing only the marginal posterior distributions for each disease.
One obvious challenge for dealing with configurations, is that the number of models that needs to be considered for each disease is already large, and the number of possible configurations is the product of these. This implies that exponentially increased computational time and memory will be required to evaluate all configurations, and to store these results. We provide solutions for both challenges. First, we show the log Bayes factor for a multinomial model that simultaneously considers all diseases can be approximated by a quantity that can be rapidly calculated - the sum of the log Bayes factors for the corresponding logistic models for each individual disease and an offset term determined by sample and model sizes (Supplementary Note). Second, we show that the marginal (single disease) model posteriors from the multinomial model can be calculated without needing to store the individual configuration Bayes factors (Supplementary Note). This enables us to work directly with the log Bayes factors of individual logistic disease models as input, and to store only the marginal model posterior probabilities for each disease, as derived from the multinomial model, solving both computational time and memory challenges: joint analysis of 2-6 diseases in the IL2RA region, (after individual stochastic search results were generated with GUESSFM), took 15-83 seconds. When the multinomial is inappropriate for all samples, for example because case samples come from multiple populations, with not all populations represented for all diseases, we fit a multinomial to the samples from common populations, and add disease-specific log Bayes factor terms from a logistic model fitted to the distinct populations.

Finally, to enable interpretation of the posterior probability of thousands of models for each disease, which typically contain many models differing only by the exchange of one SNP for another in high LD, we formalize the method for grouping SNPs across multiple diseases by hierarchical clustering of SNPs according to their LD ($r^2$) and the probability of being jointly required to explain disease, grouping SNPs selected with some nominal posterior probability which are in high LD and rarely selected together in any model (Supplementary Note).
MFM increases chance of selecting the correct model

We examined the performance of MFM by simulation. We found that when causal variants overlapped between diseases, MFM was able to recover the correct models at smaller sample sizes than individual disease analysis (Fig. 4a-b, Supplementary Tables 12, 13), i.e. sharing information between diseases contributed to a gain in accuracy similar to increasing sample size for each disease. When no causal variants were shared, multinomial and independent approaches generally gave very similar results (Fig. 4c, Supplementary Table 14), i.e. sharing information did not tend to mislead as long as there were strong signals in each disease. In the case that one disease had no associations in the region, the multinomial analysis results were very close to independent stochastic search results for the associated disease (Fig. 4d, Supplementary Table 15); i.e. no information is gained by upweighting shared causal variants between the diseases but there is also no noticeable loss in accuracy in doing so.
Figure 4: Comparison of MFM analysis and single disease analysis. a,b MFM (solid lines) can identify the true two causal variant model at smaller sample sizes than independent analysis (dashed lines) in simulated data when there is sharing between diseases. c,d When there is no sharing (c) or one disease has no true associations (d), no information is gained by using MFM but there is only minimal loss in accuracy in doing so. Causal variants were simulated for two diseases with equal effect size with models defined by SNP groups from the IL2RA region. Throughout, disease 1 has causal variants A+D, while causal variants for disease 2 vary. a “A>D, A>C” disease 2 has causal variants A+C; odds ratios for a variant if causal are A: 1.4; C: 1.25; D: 1.25. b “A<D, A<C” as for a but with odds ratios A: 1.25; C: 1.4; D: 1.4. c disease 2 has only C causal; odds ratios A: 1.25; C: 1.25; D: 1.25. d disease 2 has no causal variants (no association).
We applied MFM to all 30 ImmunoChip regions with at least two associated diseases (complete results in Extended Information and Supplementary Table 16). We identified seven regions for which the top model by single disease stochastic search and MFM differed (Table 2). Four of these were single SNP models under single disease analysis which moved to an alternative single SNP in joint analysis. For three of these four, the difference was seen in analysis of a UK-only subset, so that we could consider single-disease analysis of the UK+international data which included more samples but used the more conventional analysis method as an “adjudicator”. In all three cases, this adjudicator matched the MFM analysis of the UK-only data, suggesting that UK single disease analysis was limited by power, and that UK MFM analysis increased power, allowing conclusions to be drawn that were consistent with those seen in a larger single disease analysis.

One of the multi-SNP regions which showed differences across multiple diseases was on chromosome 2q, harbouring the candidate gene CTLA4. In stepwise analysis, iRA, T1D, ATD, and CEL all converge on a single SNP model, in the group labelled G in the stochastic search results, while for iCEL a single SNP is selected in group I (Table 3, Fig. 5a). For single disease stochastic search, we find CEL (UK only) and ATD have a single signal in the group labelled G, matching the stepwise results, while RA and T1D both have 2 signals, in groups labelled E and H. The iCEL result is more uncertain, with the posterior spread between I+K, I or E+G. Note that K is also the second selected SNP for iCEL stepwise regression (p=4x10^-6), though it doesn’t reach our adopted significance threshold. Simulations show that G may tag an E+H model (Fig. 5b-c, Supplementary Tables 8-9).

MFM finds increased support for E+H for RA and T1D while the CEL and iCEL results become more concentrated with support for G or E+G (Table 3). While we suggested G may tag E+H, MFM
maintains strongest support for G in ATD, although there is also posterior support for H in combination with other groups (group marginal posterior probability of inclusion, gMPPI=0.60). A previous attempt to fine map autoimmune disease association, by colocalization analysis of T1D, RA and CEL (using the same UK data as here) came to similar conclusions, finding strong support for E+H models for iRA and T1D and either G or E+G for CEL\textsuperscript{1}. However, a more recent analysis of T1D and RA, also in largely the same samples, identified a different pair of variants, rs3087243 (G) and rs117701653 (C)\textsuperscript{19} for both diseases using an exhaustive search of all one and two SNP models.

We compared the models suggested by all these studies across all diseases by BIC (Supplementary Table 17) and using haplotype analysis (Fig. 5d). This visually highlighted rs117701653/C identified for iRA by exhaustive search\textsuperscript{19} and rs76676160/K identified by stochastic search for CEL and iCEL as having similar protective effects across all diseases and low minor allele frequencies (<0.05). The two SNPs are unlinked ($r^2<0.01$) and in low LD with other genotyped or imputed SNPs outside their groups ($r^2<0.2$). The 2-SNP models E+H identified here, and G+C\textsuperscript{19} have similar BIC in our data for iRA and iCEL (Supplementary Table 17), but the greater number of SNPs in the E and H groups mean that E+H encompasses many more possible causal variant pairs and so has greater grouped posterior support. Additionally, individual E+H models have a clearly better fit than G+C for T1D (Supplementary Table 17). In total, results in this region exemplify the difficulty with fine mapping multiple causal variants in the presence of complex LD, and suggest the region likely contains 3 common causal variants, in groups E (CEL, RA, T1D), G (CEL and ATD) and H (RA and T1D, and possibly ATD) and possibly two low frequency causal variants in groups C and K (RA, CEL).
Figure 5: Analysis of chromosome 2q region containing CTLA4

a Map showing positions of SNPs (GRCh37) colour-coded by SNP group. SNPs in the same group are in high LD. b Comparison of stepwise and stochastic search applied to simulated data. Causal variants were simulated as follows: “G”: single causal variant G, OR=0.1.25; “E+H” causal variants E+H, odds ratios E:1.19, H:1.24 (observed in T1D data); “E>H”: causal variants E+H, odds ratios E:1.24, H:1.19. The y axis shows the proportion of simulations in which the stepwise approach chose the indicated model (adding SNPs while p < 10^{-3}) or the average posterior probabilities for each model for the stochastic search approach. Sample size (x axis) is the number of cases and controls. c Assuming E and H are causal, this plot shows the probability that G has the smallest p value as a function of the effect sizes (log odds ratios) at E and H. The estimated effects for E and H from
T1D data are shown by a point, and the simulations from b by “<” and “>” for E<H and E>H conditions respectively. d Haplotype analysis of SNP groups with support in any analysis. Each row represents one SNP, with possible alleles colour coded according to major or minor. Each column is a haplotype - a specific combination of alleles across all SNPs - with frequency in UK controls and effect on disease risk (log OR + 95% CI).

Our previous report of stochastic-stepwise mismatch focused on MS and T1D in the IL2RA region. We identified four groups of SNPs corresponding to four causal variants for T1D, with results agreeing between stepwise and stochastic search. However, while stepwise search identified a single SNP for MS, rs2104286 (group B), stochastic search identified two distinct variants in groups A and D (posterior probability 55%), and suggested that rs2104286/B was a joint tag for these groups ($r^2 = 0.334$ and 0.301, respectively), a conclusion supported by haplotype analysis and simulations here (Fig. 6, Supplementary Tables 10, 11).
**Figure 6:** Analysis of chromosome 10p region containing *IL2RA*  

- **a** Map showing positions of SNPs (GRCh37) in groups A, B and D. SNPs in the same group are in high LD, with colour used to indicate group membership.  
- **b** Haplotype analysis of SNPs selected by stepwise search and GUESSFm for MS. There are four common haplotypes. Three appear protective, carrying the minor allele at either A or D, but only two carry the minor allele at B.  
- **c** Comparison of stepwise and stochastic search applied to simulated data. Causal variants were simulated as follows: “B”: single causal variant B, OR=0.8; “A< D” causal variants A+D, odds ratios A:0.84, D:0.77; “A~ D”: causal variants A+D, odds ratios A:0.81, D:0.8 (observed in MS data); “A> D”: causal variants A+D, odds ratios A:0.77, D:0.84. The y axis shows the proportion of simulations in which the stepwise approach chose the indicated model (adding SNPs while p < 10^{-6}) or the average posterior probabilities for each model for the stochastic search approach. Sample size (x axis) is the number of cases and controls.  
- **d** Assuming A and D are causal, this plot shows the probability that B has the smallest p value as a function of the effect sizes (log odds ratios) at A and D. The estimated effects for A and D from MS data are shown by a point, and the simulations from c by “<” and “>” for A< D and A> D conditions respectively.
While our previous analysis included UK and non-UK (international) cases and controls for MS, here we used only the UK subset, and both stepwise and stochastic search identified B (group posterior probability, gpp=0.632), with the A+D model having only gpp=0.188, consistent with results that stochastic selection of a joint tag depends on sample size. A more recent stepwise analysis of a larger, international sample has identified two SNPs, rs11256593 and rs12722559\textsuperscript{20}. rs12722559 ($r^2 0.323$ with rs2104286/B) is in our group H (gpp=0.114, third strongest stochastic search model) while rs12722559 ($r^2 0.482$ with rs2104286/B, $MPPI=1.20\times10^{-5}$) did not belong to any of our SNP groups. In our UK data, we found the best fitting models were A+D (BIC 19299.46) and B (19302.88), both significantly better fits than rs11256593+rs12722559 (BIC 19320.06).

For ATD, stepwise search identified a 1-SNP model, rs706779/J, consistent with previous analyses of ATD\textsuperscript{12,21}, and matching the top reported SNP for another IMD, Vitiligo\textsuperscript{22}, while stochastic search selected a two SNP model, A+C (Table 1, Supplementary Table 18). MFM maintained support for the A+C model for ATD, and preferred the 2-SNP A+D model for MS (extended data pages 187-191), agreeing with our previous stochastic search results for a larger UK + international MS dataset\textsuperscript{8}. Limited power may also affect RA-international in this region, for which individual analysis picked group I (97%) and MFM support was split between groups A (20%) and I (70%).

Our results emphasize the importance of the A group, which is selected for three of the four diseases (T1D, MS, ATD). This group of SNPs have been previously associated with variation in the expression of IL2RA mRNA and of its encoded protein, CD25, in CD4\textsuperscript{+} memory T cells\textsuperscript{23,24}, and a recent allele-specific expression study has pinpointed the causal variant affecting mRNA expression among the set as rs61839660\textsuperscript{25} - notably the same variant identified in an IBD GWAS of 67,852 individuals\textsuperscript{26} and an eczema/dermatitis phenotype in a GWAS of thousands of
phenotypes for 337,000 samples in the UK Biobank\textsuperscript{27}, supporting the notion that this SNP has a common effect across multiple diseases that is missed in stepwise analysis of MS and ATD. We note that the \textit{direction of effect} for rs61839660 is opposite in IBD and eczema/dermatitis (risk allele T) compared to T1D, MS, ATD and JIA\textsuperscript{14} (risk allele C). We note also that the minor alleles of group I SNPs (represented by rs706778 and rs11256557 in the haplotype analysis, Extended data page 188) selected for RA-international are carried along with the minor protective alleles of groups A, C and D and it is possible that the group I SNPs are are tagging three \textit{IL2RA} SNP groups.

\textit{Allele-specific expression analysis confirms functional effects of A and D SNPs in \textit{IL2RA}}

In addition to linking group A SNPs to \textit{IL2RA} expression, we have shown that SNPs in group D decrease the percentage of CD25 expressing naive T cells\textsuperscript{8,23}. Here, we extend our analysis of \textit{IL2RA} mRNA expression to examine any effects of rs2104286/B in the context of groups A and D. Allele-specific expression assays compare relative expression between paternally and maternally inherited chromosomes in individuals heterozygous for a putative functional SNP according the the allele each chromosome carries at the SNP. It is a powerful design, because the within-individual comparison controls for between individual biological variation resulting from other genetic and environmental differences. We quantified allele-specific expression of \textit{IL2RA} mRNA in memory and naive CD\textsuperscript{4}\textsuperscript{+} T cells isolated from 36 donors selected by genotype from a bioresource (www.cambridgebioresource.org.uk) to be heterozygous at SNPs in group A (“A-het”), D (“D-het”) or both (“A+D-het”). To control for other potential effects, we chose donors homozygous for SNPs in groups C and F. The pattern of LD in the region means that the large majority of A-het and D-het individuals are also heterozygous at the B SNP and A+D-het individuals are homozygous at the B
SNP (Fig. 7a, Supplementary Table 19), allowing us to directly compare the effects of SNPs in groups A, B and D.

In memory CD4+ T cells, A-het and A+D-het individuals showed an allelic imbalance with the MS protective A haplotype producing more IL2RA mRNA, inconsistent with B causing the imbalanced expression since A+D-het individuals tested are homozygous for B (Fig. 7b). Also inconsistent with B causality is the lack of allelic imbalance in memory T cells from D-het individuals who are heterozygous at B. In naive CD4+ T cells, D-het as well as A+D-het heterozygotes had an allelic imbalance with the protective D haplotype producing less IL2RA mRNA than the susceptible or protective A haplotypes, confirming our previous observations of decreased CD25+ naive CD4+ T cells associated with donors having the protective D haplotype8. Again, this is inconsistent with B causality, since only D-het and not A+D-het individuals are heterozygous at B. In A-hets donors there is appears to be an allelic imbalance in naive CD4+ T cells favouring the A versus susceptible haplotype, which is the opposite direction to that observed with protection at D and could reflect an anticipatory differentiation of naive T cells toward the memory lineage and its phenotype of increased CD25 expression in A haplotype donors. However, it is not significant, and we did not observe an increase in CD25+ naive T cells associated with the A haplotype in a previous study23.

Additionally, we identified four individuals, three of whom carry rare IL2RA haplotypes (Fig. 7c): donor 1 carries a common haplotype combination that is homozygous across A, B, D; donor 2 carries the minor allele at B in the absence of a minor allele at either A or D, donor 3 carries a minor allele at D but not B, and donor 4 also carries a minor allele at D but not at B on one haplotype and minor alleles at A and B on the other haplotype (Fig. 7a). Neither donor 1 or 2 demonstrated an ASE in either the memory or naive T cells, an expected result for donor 1 who does not carry a minor allele at A, D or B, and a result from donor 2 showing that the minor allele at B is not associated with either phenotype. ASE results from donors 3 and 4 were consistent with
those of D-hets and A+D hets, respectively, shown in Fig. 7b, even though the status of the B SNP was different. These rare donors are consistent with our conclusions that differences seen in *IL2RA* mRNA expression are controlled by the A and D SNPs, in memory and naive CD4^+^ T cells, respectively, and argue that the B SNP tags two functionally distinct groups of SNPs, A and D.
Allele-specific expression analysis of IL2RA shows there are two phenotypes that map to the A and D SNP groups and not the B group, providing functional evidence that the stochastic search better explains the genetic association than stepwise. 

**Figure 7:** Allele-specific expression analysis of IL2RA shows there are two phenotypes that map to the A and D SNP groups and not the B group, providing functional evidence that the stochastic search better explains the genetic association than stepwise. 

**a** Schematic of donor IL2RA genotypes used in allele-specific expression studies. As the minor alleles for both A and D each usually co-occur with the minor B allele, in A-het and D-het individuals, the B SNP is heterozygous but in A+D-het individuals, the B SNP is homozygous. There are rare exceptions as seen in donors 3 and 4. 

**b** Allele-specific expression of IL2RA in CD4+ central memory T cells and CD4+ naïve T cells in A-het, D-het and A+D het donors. The allelic ratios (top:bottom haplotypes shown in panel a) are calculated from 3-4 replicates per individual. P values were calculated by T test of allelic ratio in each group compared to gDNA. Donors that contributed to panel c are indicated by a triangle. 

**c** Donors with rare IL2RA haplotypes confirm that the B SNP does not explain genotype-phenotype expression of IL2RA. As there is only one donor per genotype we cannot perform statistical testing. We show each of the four replicate allelic ratios (ratio order as in panel b) to indicate the variability of the assay.
Discussion

Fine mapping is a general problem in statistical genetics, important in its own right and for informing integrative downstream analyses. We have shown that there are candidate causal SNP models for which stepwise regression does not converge to the correct solution, even as the sample size grows, and described the constraints on LD that give rise to this joint tagging phenomenon. In contrast, stochastic searches do tend to the correct solution as sample sizes increase, and we propose they should be more widely adopted by those interested in fine mapping GWAS results. However, even stochastic search methods are limited by existing sample sizes when there are multiple causal variants in proximity, and may produce similar results to stepwise methods when sample sizes are insufficient.

Our new method MFM borrows information across diseases and is thus related to, but distinct from, methods which aim to assess whether two diseases share causal variant(s) in a region or which fine map those variants conditional on evidence for shared causal variants. We avoid enforcing identity of causal SNPs or their effect sizes between different diseases, as in analysis of an overarching disease phenotype (eg “autoimmune disease”). It is clear from our results that, causal variants may differ between diseases in the same region and that, even when causal variants are shared, effect sizes and even direction of effects may differ between diseases. While we use individual level genotype data from IMD studies, the method could be adapted to summary GWAS data with Bayes factors calculated using summary data or applied to other collections of diseases where causal variants may tend to be shared, such as psychiatric diseases or metabolic-related traits.

One key result from our analysis is that sample sizes in the low tens of thousands may still not be large enough to robustly fine map multiple causal variants. This motivates continued collection of
GWAS samples for diseases too infrequent to be found in large numbers in the Biobank style datasets, and greater sharing of data between researchers working on related diseases to better map the most likely genetic causal variants. A particular note of caution is raised by the genomic locations where we find discrepancies between stochastic and stepwise results. These are almost entirely those with the strongest biological prior for involvement in these diseases, and also those with typically the strongest effects, and thus greatest power. We question whether these regions are most likely to give rise to discrepancies because they harbour the largest numbers of potential effects or whether, if we had access to much larger datasets, we would see similar discrepancies genomewide.

Our analysis of six diseases reveals several cases where there appear to be multiple functional haplotypes - ie more than one IMD causal variant in a region - that affect different diseases differently. Thus, these functional haplotypic maps are essential for designing biological follow-up experiments, for which we need to decide not just what variants to test, but also what variants to hold constant to avoid confounding the effect of the variant of immediate interest. Note that in our ASE work, testing of B heterozygotes, which are in fact a 2:1 mix of D heterozygotes and A heterozygotes, would have resulted in bimodal results in both the memory and naive CD4+ T cells subsets. The ability of the stochastic search to suggest alternative models provided us the knowledge to compare such models biologically, thereby allowing homogeneous phenotypic groups to emerge that were differently associated with the A and D SNP groups. Our approach can be expanded in a haplotype-directed manner to other accessible immune cell types to determine cell-specific and activation-specific influences of each disease-associated SNP group (A, C, D, E, F) on IL2RA mRNA expression, enabling a more complete picture of how particular haplotypes mediate protection or susceptibility to disease. The association of the minor alleles of the A haplotype with disease protection in the case of T1D, MS and ATD, but with disease susceptibility for eczema and IBD, could be caused by A-mediated regulation of IL2RA expression in two
different cell types: one critical for T1D, MS and ATD disease pathogenesis, the other type pivotal for eczema and IBD. Alternatively, the genetically-determined level of CD25 on memory CD4 T cells could influence their likelihood of differentiating into particular types of cytokine-producing effector cells, a phenotype beneficial for some diseases but not others. We propose that, rather than attempting to colocalize eQTL signals and disease associations that are both determined by stepwise analysis\textsuperscript{32}, disease haplotype-directed searches for allele-specific expression exemplified in this study will lead to greater clarity when unraveling cellular mechanisms in immune-based diseases.

Methods

Simulations - single trait

Simulations were carried out under a realistic scenario that mimics the MAF and $r^2$ in the $IL2RA$ region. We simulated haplotypes for 345 SNPs in chromosome 10p-6030000-6220000 (GRCh37/hg19), based on the CEU 1000 Genomes Phase 3 data\textsuperscript{33} (ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/release/20130502/) using HapGen2\textsuperscript{34}. Code to perform the simulations can be found in https://github.com/jennasimit/MFMextra. Causal variants were selected within SNP groups for each disease model (see Supplementary Table 18) with various OR relating the odds of disease in heterozygote carriers of the non-reference allele compared to the homozygote reference allele. We assumed a multiplicative model throughout. The SNPs belonging to the above-mentioned groups, as well as the lead SNPs for autoimmune thyroid disease (ATD; rs706799), alopecia areata (AA; rs3118470), rheumatoid arthritis (RA; rs10795791), and ulcerative colitis (UC; rs4147359) were extracted from the generated data for analyses via stepwise regression and stochastic search; the lead SNP for multiple sclerosis forms group B. For each replication a stepwise regression model was fit, adding SNPs to the model using a p-value threshold of $1\times10^{-6}$. To generate stochastic search results, we used GUESSF\textsuperscript{8}, setting
a prior of 3 causal variants for the region to encourage good mixing of the chains in the initial
Bayesian variable selection, and setting the prior to a more conservative 2 causal variants per
region to obtain final model posterior probabilities (PP). Model fits were summarized by the
proportion of times each model was selected via stepwise regression or the mean of the
GUESSFM posterior probabilities for each model.

Simulations - multiple traits

We adapted the HapGen2 simulation outlined above to simulate datasets for two case and one
control set; code is available in https://github.com/jennasimit/MFMextra. First we used HapGen2 to
generate a population of 100,000 individuals based on the CEU 1000 Genomes Phase 3 data.
Causal variants for each trait were randomly selected within particular SNP groups for a certain
disease model (see Supplementary Table 18); when the same SNP group contained a causal
variant for both diseases, one variant was selected from the group and set as causal for both
diseases. Logistic regression models with the selected causal variants and odds ratios (OR) were
then used to assign each individual as either a member of the controls, disease 1 cases, or
disease 2 cases until the desired number of individuals in each group was attained; let OR_{jk} be the
odds ratio for causal variant j and disease k. The prevalence for both diseases was set to 0.1, as
our purpose is to generate cases and controls for method comparison. In particular, the following
steps were used to ascertain control/disease 1/disease 2 status, where x_{ij} is the number of non-
reference alleles of variant i for individual j (i.e. genotype score), g_j is the vector of genotype scores
for individual j, \beta_0 = \log(0.1), and \beta_{ik} = \log(OR_{ik}) is the effect of causal variant i for disease k.

1. Let n_k be the number of individuals ascertained to group k (controls are group 0, groups 1
and 2 consist of members with disease 1 and 2, respectively) and G_k be the matrix of
genotype scores for individuals in group k. Initialize n_k=0 and G_k as a null vector.

2. Set j=1 and repeat the following steps while n_0 < N_0 or n_1 < N_1 or n_2 < N_2.

   a. For k=1,2 determine p_{jk} = \text{logit}^{-1}(\beta_0 + \sum_{i=1}^{m_1} \beta_{ik} x_{ij}) and generate uniform
random variables $u_1, u_2$.

b. If $u_1 > p_1$ and $u_1 > p_2$, then $n_0 = n_0 + 1$, append $g_j$ to $G_0$, $j=j+1$, and go to beginning of step 2.

c. Else, if $u_1 \leq p_1$ and $u_1 > p_2$, then $n_1 = n_1 + 1$, append $g_j$ to $G_1$, $j=j+1$, and go to beginning of step 2.

d. Else, if $u_1 \leq p_2$ and $u_1 > p_1$, then $n_2 = n_2 + 1$, append $g_j$ to $G_2$, $j=j+1$, and go to beginning of step 2.

e. Else, if $u_2 < 0.5$ and $n_1 < N_1$, then $n_1 = n_1 + 1$ and append $g_j$ to $G_1$, $j=j+1$.

Otherwise, $n_2 = n_2 + 1$ and append $g_j$ to $G_2$, $j=j+1$. Go to beginning of step 2.

3. Keep the first $N_k$ rows from $G_k$, $k=0,1,2$.

We simulated either shared configurations where each disease was under the influence of two causal variants, one shared between diseases (A) and one unique to each disease (one from C, one from D); or independent configurations, where the two diseases were under the influence of distinct causal variants (one from each of A and D for one disease and one from C for the other disease) or one disease had no associations in the region (one from each of A and D for one disease and none for the other disease). All causal variants were assigned an odds ratio of 1.25 or 1.4. For both diseases, equal-sized case-control samples consisting of N cases and N controls were considered for N ranging from 1000 to 5000; each simulation setting had 100 replications.

We compared the independent stochastic search analyses of each disease with the multinomial approach with upweighted sharing based on a range of target odds (i.e. prior odds of no sharing of causal variants between one disease and any other disease). We focused on a target odds (TO) of 1, such that there is an equal probability of sharing to non-sharing. Results for a range of TO from 9 (no sharing more likely than sharing of causal variants) to 0.35 (sharing more likely than distinct causal variants) are in Supplementary Tables 12-15.
Mathematical predictions of SNP with minimum univariate p value

We used “sunbeam plots” to characterize how changing the odds ratio of two causal SNPs in a model can change the probability that a third variant will have the minimum p-value (and hence be selected first in any stepwise fine mapping algorithm). We utilized components of the simGWAS package (http://github.com/chriswallace/simGWAS) to calculate expected GWAS Z scores for any given set of causal variants and their effect sizes, across those causal variants and their neighbouring SNPs. We considered the behaviour of Z scores at each of two nominated “causal” variants (following Fig. 1, let us refer to these variants as A and C) with a third SNP, not itself causal, but potentially correlated with both A and C (in Fig. 1, this is SNP J). For each of a range of possible odds ratios, we computed which of the three SNPs had the smallest expected p-value, and coloured that square of the grid correspondingly. When the log odds ratios of both A and C were close to 0, then no SNP had a low p-value and it was not possible to find significant evidence of disease association in the region. This section of the grid was coloured white. Superimposed upon the grid is a point corresponding to the odds ratio we computed for A and C from the real dataset. Code to produce these plots is at https://github.com/chriswallace/MFM-paper/tree/master/sunbeams.

Fine mapping analyses of ImmunoChip-genotyped diseases

We collated individual genotype data generated using the ImmunoChip for a total of 61,641 individuals, formed of controls and six disease cohorts: MS (UK subset), T1D, juvenile idiopathic arthritis (JIA, UK subset), celiac disease, rheumatoid arthritis (RA) and autoimmune thyroid disease (ATD) (Supplementary Table 1). All genome coordinates are from build GRCh37. To ensure controls could be combined across datasets, we restricted analysis for the multinomial model to UK samples, and used principal component analysis including 1000 Genomes data to
exclude 2 individuals who fell outside individual country clusters. Genotypes were compared
between datasets to ensure exclusion of duplicate samples. Data were split into subsets according
to the densely genotyped regions targeted by the ImmunoChip (Supplementary Table 2) and
imputed to 1000 Genomes phase 3\textsuperscript{33} using SHAPEIT\textsuperscript{36} and IMPUTE2\textsuperscript{37}. Phased reference data
was downloaded from https://mathgen.stats.ox.ac.uk/impute/1000GP_Phase3.html. Country and
the first 4 principal components were included as covariates in all regressions to account for
population structure. SNPs were excluded if they had info scores < 0.3, certainty < 0.98, |Z| for
HWE > 4 in UK controls, MAF < 0.5% in UK controls, call rate < 0.99 in any case or control group,
or an absolute difference in “certain genotype” call rates between controls and any case group of >
5%. Forward stepwise regression was performed using univariate logistic regressions across all SNPs
in the region. The SNP with the strongest association (smallest p value) was selected, then all two
SNP models containing the selected SNP and any other SNP were considered, and the process
repeated until no SNP could be added with a marginal p < 10\textsuperscript{-6}.

Stochastic search fine mapping of single diseases was performed using GUESSFM
(\url{http://github.com/chr1swallace/GUESSFM}). Initial searches were performed after tagging at
r\textsuperscript{2}<0.99 with an optimistic binomial prior for the number of causal variants per region with
expectation set at 3 to allow good mixing of the chains. Reanalysis of the expanded tag sets for
SNPs in models included in the model set with total posterior probability 0.99 was performed using
approximate Bayes factors and the more conservative prior expectation of 2 causal variants per
region using GUESSFM. GUESSFM results were combined using the methods proposed in this
paper, as implemented in the R package MFM (\url{http://github.com/jennasimit/MFM}). We set the
prior odds that two diseases shared any causal variants to 1 (ie a 50% probability that they share
none). For a number of diseases, \(d > 2\), we set the prior that the diseases share no causal variants
to $0.5\sqrt{d-1}$, where the exponent is the geometric mean of the exponents in the (nonsensical)
extremes $0.5^{d-1}$ which assumes all diseases are independent and $0.5$ which assumes all diseases
are completely dependent.

Code to perform these steps is available at [https://github.com/chr1swallace/MFM-analysis](https://github.com/chr1swallace/MFM-analysis).

**SNP grouping**

SNPs with marginal posterior probability of inclusion > 0.001 were grouped according to criteria of
substitutability - that one SNP could substitute for another in all models. We reasoned that this
meant SNPs would need to be in LD - high $r^2$ - and rarely selected together in models - i.e. model
selection correlation ($r$) should be negative. We hierarchically cluster SNPs within each disease
according to $r^2 \times \text{sign}(r)$ using complete linkage, and group SNPs by cutting the tree such that all
SNPs within a group must have pairwise $r^2 > 0.5$, pairwise $r < 0$, and marginal posterior probability
that both are included in a model was < 0.01. We then identify overlapping groups defined in
different diseases, and merge or split groups when they meet this criteria. The specific algorithm is
defined in the group.multi function in
[https://github.com/chr1swallace/GUESSFM/blob/master/R/groups.R](https://github.com/chr1swallace/GUESSFM/blob/master/R/groups.R).

**Haplotype analyses**

Haplotype analyses were performed by first phasing the genotypes across selected SNPs using an
E-M algorithm and selecting 10 multiply imputed samples from the posterior ([snphap],
[https://github.com/chr1swallace/snphap](https://github.com/chr1swallace/snphap)). These samples were analysed in parallel and results
combined using standard multiple imputation functions in the R package MICE. Code to
implement these steps is available at [https://github.com/chr1swallace/snpHaps](https://github.com/chr1swallace/snpHaps). All analyses
included the first 4 PCs, and country as an additional covariate for iCEL and iRA to account for
population structure.

Allele-specific expression

The NHS Cambridgeshire Research Ethics committee approved work involving human participants for allele-specific expression assays. Samples were obtained from the Cambridge BioResource (www.cambridgebioresource.org.uk) as part of the 'Genes and Mechanisms of Type 1 Diabetes' study and were of self-reported white ethnicity. Informed consent was obtained from all volunteers for the collection and use of the peripheral blood samples. Data and samples are always treated anonymously and confidentially. Allele-specific expression analysis was performed as described in Burren et al., 2017 but modified to start with sorted CD4+ naive and central memory T cells. CD4+ naive T cells were sorted as CD3+ CD4+ CD8- CD127 med/high CD25 low-med CD45RA+ and CD27+, whereas CD4+ central memory T cells were sorted as CD3+ CD4+ CD8- CD127 med/high CD25 low-med CD45RA- and CD27+.

To phase the direction of effect from the four donors carrying rare IL2RA haplotypes (Fig. 7a, 7c), their haplotypes were compared to those found in the 1000 Genome Project CEU data to assess the allele frequency of the ASE readout SNP (rs12244380, A or G), to predict which allele is most likely to be carried. For donor 1, the E haplotype carries the G allele with frequency 73% whereas the susceptible haplotype carries the A allele 60% of the time. For donor 2, it is most likely the B and E alleles are on the same haplotype (20 examples where they are together vs 4 examples where they are on different chromosomes), and here the B+E haplotype carries the A allele of rs12244380 (100%). For donor 3, all examples of the D haplotype lacking the B allele carry the A allele of rs12244380 (14/14), whereas the E haplotype carries the G allele of rs12244380 73% of the time. Lastly, for donor 4, the A haplotype carries the G allele of rs12244380 88% of the time, and for all examples of the D haplotype lacking B carries the A allele of rs12244380 (7/7). Where multiple assays were performed on the same donor, we retained those with the smallest standard
deviation of allelic ratios, but show both results in Supplementary Table 19.

**URLs**

Global Biobank Engine, Stanford, CA ([http://gbe.stanford.edu/](http://gbe.stanford.edu/)) [accessed January 2018].

Extended information in searchable format at [https://chr1swallace.github.io/MFM-output](https://chr1swallace.github.io/MFM-output).

**Code Availability**

Multinomial Fine-mapping (MFM) software is could be found at [https://jennasimit.github.io/MFM](https://jennasimit.github.io/MFM).

Custom code for our analyses is available at [https://github.com/chr1swallace/MFM-analysis](https://github.com/chr1swallace/MFM-analysis).

**Data Availability**

Data was obtained from the study authors for each of the six autoimmune diseases that we analysed. There are no restrictions for data access and the following may be requested from the original study authors: ATD ImmunoChip, Cooper et al. (https://www.ncbi.nlm.nih.gov/pubmed/22922229); RA ImmunoChip, Eyre et al. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3882906/); JIA ImmunoChip, Hinks et al. (https://www.ncbi.nlm.nih.gov/pubmed/23603761). MS ImmunoChip data was accessed through application to the International Multiple Sclerosis Genetic Consortium (IMSGC; http://www.imsgenetics.org/). Primary analysis of these data is presented by Mayes et al. (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3882906/) and the dbGaP accession number for the US cohort is phs000357.v2.p2. The primary analysis of the Celiac ImmunoChip is by Trynka et al. (https://www.nature.com/articles/ng.998) and the genotype data is hosted by the European Bioinformatics Institute, under accession number EGAS00000000053. T1D ImmunoChip data is available from dbGaP (Study Accession: phs000180.v3.p2) and 2000 T1D samples were genotyped as part of the WTCCC (and controls) - data access is described at [https://www.wtccc.org.uk/info/access_to_data_samples.html](https://www.wtccc.org.uk/info/access_to_data_samples.html).

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Author Contributions

JA developed the MFM method, performed statistical analyses and interpreted results, wrote the paper. DR performed ASE assays and analysis and interpreted results, wrote the paper. MF performed mathematical analyses and conceived the sunbeam plots. NG performed mathematical analyses and verified the analytical methods. LW supervised ASE work, interpreted the results of ASE analyses and all the fine mapping analyses, wrote the paper. CW conceived the study, developed the MFM method, performed statistical analyses and interpreted results, wrote the paper. All authors read and agreed the manuscript.
### Table 1: Regions that have conflicting models selected by stepwise and stochastic search for at least one autoimmune disease.

Each row summarizes results for a single region, defined by chromosome, start and end coordinates (hg19), with neighbouring or previously reported candidate gene names shown for orientation. Each stepwise search model consists of a single SNP and we also indicate which SNP group it belongs to, by a letter in front of the SNP rs ID; the SNP group size, p-value of the SNP, and stochastic search group posterior probability (GPP) are also given. Analogous information is given for stochastic search models and for 2-SNP models the joint p-values from these model are given. The LD column lists the $r^2$ between the stepwise SNP and the SNP(s) from the stochastic search model.

| Region | Disease | Stepwise | Stochastic |
|--------|---------|----------|------------|
|        |         | Model    | P-value(s) | SNP group size(s) | Model | P-value(s) | Stochastic GPP | SNP group size(s) | LD |
| 2q-100544954-101038647 (AFF3) | iRA | A/rs10209110 | 3.79×10⁻⁹ | 0.427 | 32 | C/rs13415465 | 1.96×10⁻⁶ | 0.514 | 93 | 0.46 |
| 2q-231076289-231235886 (SP110, SP140, SP140L) | iCEL | C/rs62192167 | 8.49×10⁻⁷ | 0.374 | 4 | B/rs12694846 | 3.62×10⁻⁶ | 0.44 | 18 | 0.12 |
| 7p-50246236-50365063 (IKZF1) | T1D | A/rs2168587 | 8.10×10⁻⁷ | 0.123 | 1 | D/rs17552787 | 2.46×10⁻⁶ | 0.457 | 20 | 0.094 |
| 7p-50366637-50694384 (DDC, FIGNL1, GRB10, IKZF1) | T1D | B/rs34046423 | 2.08×10⁻¹⁰ | 0.226 | 35 | A/rs10264390 | 2.89×10⁻⁹ | 0.657 | 37 | 0.4 |
| 15q-67414055-67469568 (SMAD3) | iCEL | A/rs2289261 | 2.48×10⁻⁷ | 0.324 | 15 | B/rs8024330 | 1.74×10⁻⁶ | 0.342 | 20 | 0.24 |
| Chromosomes | Genes | T1D Risk Allele | P-Value | Minor Allele Frequency | T1D A-allele Carrier | A-allele Frequency | iRA Risk Allele | P-Value | Minor Allele Frequency | iRA A-allele Carrier | A-allele Frequency | "10p-6030000-6220000 (IL2RA)" | ATD Risk Allele | P-Value | Minor Allele Frequency | ATD A-allele Carrier | A-allele Frequency | "14q-101290463-101328739 (MEG3)" | T1D Risk Allele | P-Value | Minor Allele Frequency | T1D A-allele Carrier | A-allele Frequency |
|-------------|-------|----------------|---------|------------------------|----------------------|------------------|-----------------|---------|------------------------|----------------------|------------------|-----------------------|-----------------|---------|------------------------|----------------------|------------------|-----------------------|-----------------|---------|------------------------|----------------------|------------------|
| 20p-1497197-1689461 (SIRPD/SIRPB1) | T1D | B/rs202535 | 6.79x10^-9 | 0.221 | 9 | C/rs202536 | 1.25x10^-8 | 0.391 | 21 | 0.49 |
| 2q-204446380-204816382 (CTLA4) | T1D | G/rs3087243 | 3.89x10^-17 | 0.00281 | 32 | H/rs231779 + E/rs370078940 | 2.10x10^-21 | 1.36x10^-8 | 0.765 | 52 | 0.50 | 0.07 |
| | iRA | G/rs3087243 | 1.54x10^-7 | 0.00787 | 32 | H/rs34029700 + E/rs7422494 | 7.04x10^-9 | 4.39x10^-9 | 0.753 | 52 | 0.26 | 0.05 |
| 4q-122973062-123565302 (IL2/IL21) | T1D | D/rs77516441 | 3.97x10^-14 | 0.0193 | 13 | F/rs13122213 + A/rs6837165 | 1.05x10^-9 | 3.43x10^-16 | 0.85 | 53 | 0.20 | 0.23 |
| 10p-6030000-6220000 (IL2RA) | ATD | J/rs706779 | 4.63x10^-6 | 0.011 | 2 | C/rs2476491 + A/rs61839660 | 2.89x10^-9 | 1.96x10^-8 | 0.954 | 8 | 0.34 | 0.13 |
| 14q-101290463-101328739 (MEG3) | T1D | C/rs34552516 | 9.69x10^-10 | 0.0814 | 5 | B/rs10540000 + A/rs11160606 | 1.13x10^-11 | 2.36x10^-8 | 0.777 | 5 | 0.29 | 0.30 |
Table 2: Regions that have conflicting models selected by stochastic search and MFM for at least one autoimmune disease. Each row summarizes results for a single region, defined by chromosome, start and end coordinates (hg19), with a previously reported candidate gene name shown for orientation. The best model for each method is selected by group posterior probability and for each method the best SNP models for each group(s) are given as representatives of the group models. The last column gives the mean $r^2$ between the SNP group(s) of stochastic search and those of MFM. The other diseases that were used in MFM are listed under Other Diseases.

| Region          | Disease | Other Diseases | Independent | MFM              | Mean $r^2$ between groups |
|-----------------|---------|----------------|-------------|------------------|--------------------------|
| 1p-2406887-2785671 (MMEL1, TNFRSF14) | RA      | CEL, MS         | D/rs4648662 | C/rs10752749     | 0.36                     |
|                 |         |                 |             | C/rs10797431     |                          |
|                 | iRA     | iCEL, MS        | C/rs141426426 | C/rs72928038     |                          |
| 6q-90806835-91039808 (BACH2) | RA      | ATD, T1D        | G/rs56258221 | C/rs72928038     | 0.33                     |
|                 |         |                 |             | C/rs72928038     |                          |
|                 | iRA     | ATD, T1D        | C/rs72928038 | C/rs72928038     |                          |
| 18p-12738413-12924117 (PTPN2) | CEL     | T1D             | F/rs34799913  | C/rs12967678     | 0.4                      |
|                 |         |                 |             | C/rs12967678     |                          |
|                 | iCEL    | iRA, T1D        | C/rs67878610 | C/rs12967678     | 1                        |
| 7p-37363978-37440453 (ELMO1) | MS      | CEL             | A/rs1962401   | C/rs77801025     |                          |
|                 |         |                 |             |                 |                          |
| 2q-204446380-204816382 (CTLA4) | iCEL    | ATD, iRA, T1D   | I/rs2162610 + K/rs76676160 | G/rs3087243 + E/rs3116499 | I 0.14 0.31  |
|                 |         |                 |             |                 |                          |
|                 |         |                 |             |                 |                          |
| 10p-6030000-6220000 (IL2RA) | MS      | ATD, iRA, T1D   | B/rs2104286/   | A/rs12722496 + D/rs7089861 | 0.2 0.3      |
|                 |         |                 |             |                 |                          |
| 16p-11017058-11307024 (DEXI) | MS      | T1D             | A/rs11643622   | B/rs12708716 + D/rs4780346 | 0.3 0.3      |
Table 3: Summary results for ATD, CEL, iCEL, iRA and T1D in 2q-204446380-2048163 (CTLA4). For each disease, the following are provided: selected stepwise model and conditional SNP p-values, high PP models (and PP) for each of stochastic search, MFM (UK samples only) and MFM with international samples.

| Disease | SNP     | P         | Stepwise Model | Independent Model | Joint (UK) Model | Joint (Int) Model |
|---------|---------|-----------|----------------|-------------------|------------------|-------------------|
| ATD     | G/rs11571297 | 1.22×10^{-24} | G 0.842 | G 0.593 | G 0.374 |
|         |         |           | G+H 0.349 | H+I 0.273 | G+H 0.236 |
|         |         |           | E+H 0.102 |          |          |
| CEL     | G/rs3087243 | 1.48×10^{-12} | G 0.641 | G 0.517 |         |
|         |         |           | G+K 0.136 | E+G 0.281 |          |
| iCEL    | I/rs2162610 | 3.74×10^{-14} | I+K 0.351 | E+G 0.829 |         |
|         |         |           | I 0.14 |          | E+G 0.115 |
| iRA     | G/rs3087243 | 1.54×10^{-7}   | E+H 0.753 | E+H 0.805 |         |
|         |         |           | A+E+H 0.142 |          |          |
| T1D     | G/rs3087243 | 3.89×10^{-17} | E+H 0.765 | E+H 0.687 | E+H 0.904 |
|         |         |           | G 0.135 |          |          |
Table 4: Summary results for ATD, MS, iRA and T1D in 10p-6030000-6220000 (*IL2RA*). For each disease, the following are provided: selected stepwise model and conditional SNP p-values, high posterior probability PP models (and PP) for each of stochastic search, MFM (UK samples only) and MFM with international samples.

| Disease | SNP       | Stepwise  | Independent | Joint (UK) | Joint (Int) |
|---------|-----------|-----------|-------------|------------|-------------|
|         |           | P         | Model PP    | Model PP   | Model PP    |
| ATD     | J/rs706779| 4.63×10⁻⁸ | A+C 0.954   | A+C 0.985  | A+C 0.986   |
|         |           |           | A+C 0.954   | A+C 0.985  | A+C 0.986   |
|         | B/rs2104286| 1.13×10⁻¹³| B 0.632     | A+D 0.883  | A+D 0.901   |
|         |           |           | A+D 0.188   | A+D 0.883  | A+D 0.901   |
| MS      | I/rs706778| 7.55×10⁻⁸ | I 0.966     | I 0.695    | A 0.201     |
|         |           |           | I 0.966     | I 0.695    | A 0.201     |
| iRA     | A/rs61839660| 3.60×10⁻³⁴| A+C+E+F 0.622| A+C+E+F 0.684| A+C+E+F 0.674|
|         | C/rs11594656| 5.85×10⁻¹²| A+E+F+H+I 0.201| A+E+F+H+I 0.178| A+E+F+H+I 0.191|
| T1D     | E/rs12220852| 8.79×10⁻¹⁰|             |             |             |
Supplementary Table Legends

Supplementary Table 1: Autoimmune disease data sample sizes by country and phenotype. We ran analyses on UK-only (ATD, CEL, JIA, MS, RA, T1D) and international (all countries, iCEL, iRA) samples.

Supplementary Table 2: Selection of region-disease combinations for fine-mapping. Each of the 90 regions is listed together with chromosome, start and end positions and minimum p-values for SNP association with each of the six autoimmune diseases (UK) and for RA and CEL in international samples (iCEL, iRA). Region-disease combinations with minimum p-values < 10E-6 were selected for fine-mapping and are in bold font.

Supplementary Table 3: Stepwise results for all regions and autoimmune diseases that met criteria for fine-mapping. For each region and disease, the SNPs selected by stepwise search are listed, as well as their conditional p-value and order of selection.

Supplementary Table 4: Stochastic search results for all regions that met criteria for fine-mapping of at least one autoimmune disease. For each region, SNPs from each SNP group are listed, together with base pairs position (GRCh37/hg19 assembly), alleles, MAF in UK samples, and marginal posterior probability of inclusion. At the first SNP in each group, the marginal group posterior probability of inclusion is listed in the Total column.

Supplementary Table 5: Region-disease combinations for which the best stepwise model is nested within the best stochastic search model. The best stepwise model is listed according to the SNP group(s) that the SNP(s) belong to. Highest group posterior probability (GPP) was used to select the best model for stochastic search and the stochastic GPP is also given for the stepwise model.

Supplementary Table 6: Comparison of stepwise and stochastic search applied to case-control simulations with a single causal variant J in IL2RA. (a) Model mean posterior probability (GUESSFM; stochastic search) and (b) Mean model selection probability (stepwise regression) for simulated data having causal variant J with OR=0.8. Data were simulated with the characteristics of the IL2RA region and there were 100 replications. Sample sizes were N cases, N controls for N=1000 to 5000 and are listed by column.

Supplementary Table 7: Comparison of stepwise and stochastic search applied to case-control simulations with two causal variants, A+C, in IL2RA. (a) Model mean posterior probability (GUESSFM; stochastic search) and (b) Mean model selection probability (stepwise regression) for simulated data having causal variants A + C, odds ratios A:0.81, C:0.74 (left), A:0.74, C:0.81 (right). Data were simulated with the characteristics of the IL2RA region and there were 100 replications. Sample sizes were N cases, N controls for N=1000 to 5000 and are listed by column.
Supplementary Table 8: Case-control simulations with a single causal variant G in CTLA4. (a) Model mean posterior probability (GUESSFM; stochastic search) and (b) Mean model selection probability (stepwise regression) for simulated data having causal variant G with OR=1.25. Data were simulated with the characteristics of the CTLA4 region and there were 100 replications. Sample sizes were N cases, N controls for N=1000 to 5000 and are listed by column.

Supplementary Table 9: Case-control simulations with two causal variants, E+H, in CTLA4. (a) Model mean posterior probability (GUESSFM; stochastic search) and (b) Mean model selection probability (stepwise regression) for simulated data having causal variants E + H with odds ratios E:1.24, H:1.19 (left) and E:1.19, H:1.24 (right). Data were simulated with the characteristics of the IL2RA region and there were 100 replications. Sample sizes were N cases, N controls for N=1000 to 7000 and are listed by column.

Supplementary Table 10: Case-control simulations with a single causal variant B in IL2RA. (a) Model mean posterior probability (GUESSFM; stochastic search) and (b) Mean model selection probability (stepwise regression) for simulated data having causal variant B with OR=0.8. Data were simulated with the characteristics of the IL2RA region and there were 100 replications. Sample sizes were N cases, N controls for N=1000 to 5000 and are listed by column.

Supplementary Table 11: Case-control simulations with two causal variants, A+D, in IL2RA. (a) Model mean posterior probability (GUESSFM; stochastic search) and (b) Mean model selection probability (stepwise regression) for simulated data having causal variants A and D with odds ratios A:0.84, D:0.77 (left), A:0.81, D:0.8 (middle) and A:0.77, D:0.84 (right). Data were simulated with the characteristics of the IL2RA region and there were 100 replications. Sample sizes were N cases, N controls for N=1000 to 7000 and are listed by column.

Supplementary Table 12: Comparison of stochastic search and MFM applied to simulations of two diseases with one strong effect shared causal variant. Disease 1 was simulated to have causal variants A + D (odds ratios A:1.4,D:1.25) and disease 2 had causal variants A + C (odds ratios A:1.4, C:1.25). MFM was run at a range of target odds (TO; prior odds of no sharing of causal variants between one disease and any other disease) values to illustrate the impact of TO and with decreasing TO there is an increasing prior weight for sharing of variants; TO=null indicates no sharing and independent stochastic search analyses were run and TO=1 was the setting used in our MFM analyses.

Supplementary Table 13: Comparison of stochastic search and MFM applied to simulations of two diseases with one weak effect shared causal variant. Disease 1 was simulated to have causal variants A and D (odds ratios A:1.25,D:1.4) and disease 2 had causal variants A + C (odds ratios A:1.25, C:1.4). MFM is run at a range of target odds (TO; prior odds of no sharing of causal variants between one disease and any other disease) values to illustrate the impact of TO and with decreasing TO there is an increasing prior weight for sharing of variants; TO=null indicates no sharing and independent stochastic search analyses were run and TO=1 was the setting used in our MFM analyses.
Supplementary Table 14: Comparison of stochastic search and MFM applied to simulations of two diseases with distinct causal variants. Disease 1 was simulated to have causal variants A + D (A:1.25, D:1.25) and disease 2 had single causal variant C (OR 1.25). MFM is run at a range of target odds (TO; prior odds of no sharing of causal variants between one disease and any other disease) values to illustrate the impact of TO and with decreasing TO there is an increasing prior weight for sharing of variants; TO=null indicates no sharing and independent stochastic search analyses were run and TO=1 was the setting used in our MFM analyses.

Supplementary Table 15: Comparison of stochastic search and MFM applied to simulations of two diseases where one disease had no associations. Disease 1 was simulated to have causal variants A and D (odds ratios A:1.4, D:1.4) and disease 2 had no causal variants. MFM is run at a range of target odds (TO; prior odds of no sharing of causal variants between one disease and any other disease) values to illustrate the impact of TO and with decreasing TO there is an increasing prior weight for sharing of variants; TO=null indicates no sharing and independent stochastic search analyses were run and TO=1 was the setting used in our MFM analyses.

Supplementary Table 16: MFM results for all regions that met criteria for fine-mapping of at least one autoimmune disease. For each region, SNPs from each SNP group are listed, together with base pairs position (GRCh37/hg19 assembly), alleles, MAF in UK samples, and marginal posterior probability of inclusion from stochastic search, MFM, and MFM with international samples. At the first SNP in each group, the marginal group posterior probability of inclusion is listed in the Total column for each of these analyses.

Supplementary Table 17: Comparison of the BICs for CTLA4 SNP models fit to ATD, CEL, T1D, international-RA and international-CEL. Representative SNP models are fit from several group models and the BIC of the best fitting model for each disease is in bold. The posterior probability (PP) and group PP (GPP) are given for each SNP and SNP group model, with the highest GPP model in bold.

Supplementary Table 18: Details of IL2RA stochastic search and MFM results for ATD, MS, T1D and RA-international (iRA) and the resulting SNP groups. SNPs within each SNP group are listed, together with their base pairs position (GRCh37/hg19 assembly), alleles and MAF (based on UK controls data). Previous SNP groups (Wallace et al. 2015) are nested within our new SNP groups and these matches are marked. For both stochastic search (SS) and MFM, the marginal posterior probability of inclusion (MPPi) is given for each SNP and disease and the SNP group marginal posterior probability (Total MPPi). For MFM, ATD, MS and T1D analyses are based on UK samples, as well as the inclusion of international controls (int.ATD, int.MS, int.T1D); international RA (iRA) analyses are included, but not RA (UK only) since it did not meet our fine-mapping criteria.

Supplementary Table 19: Allele-specific expression (ASE) analysis results. The genotype of a SNP from each of the IL2RA SNP groups defined in Supplementary Table 18 is listed for each participant that ASE was performed on. The genotypes are phased so that all the SNPs listed for allele 1 are on the same chromosome, and gives directionality for the ASE readout SNP.
rs12244380, which is in the 3'UTR of IL2RA. ASE was measured using targeted NGS and the counts from each allele of rs12244380 are provided with 3-4 technical replicates performed. The average of the technical replicates was used to calculate the allelic ratio. Some samples were tested multiple times and these are highlighted in green. The allelic ratio for the central memory CD4+ T cells and naive CD4+ T cells are calculated as the ratio of A to G alleles at the readout SNP, and then re-ordered based on phased haplotypes to match the direction shown as top:bottom in the cartoon haplotypes depicted Fig. 7a. Not all samples were tested with both naive and central memory CD4+ T cells due to cell number availability. The genomic DNA samples are included as a control showing there is no bias regardless of genotype and all are reported as the ratio of the A:G allele of rs12244380.
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