Supplemental Material

Supplemental Tables

Table S3. Results of the subset-based meta-analysis for the lead variants showing evidence of opposite allelic effect across the autoimmune diseases contributing to the association signal.

Region	Position (bp)	SNP	Gene	A1	P2sided	Pheno Risk	P-value risk	OR [95% CI] risk	Pheno Protective	P-value protective	OR [95% CI] Potective
2q31.3	182,057,640	rs12619531	*ITGA4*	G	1.18E-18	CeD	1.65E-18	1.18 [1.13-1.22]	**SSc**	1.55E-02	0.92 [0.86-0.98]
3q25.33	159,647,674	rs17753641	*IL12A*	G	1.64E-29	CeD	2.69E-28	1.38 [1.30-1.46]	**SSc**	8.49E-04	0.80 [0.71-0.91]
5q33.1	150,438,988	rs1422673	*TNIP1*	T	1.87E-09	**RA** SSc	3.37E-09	1.11 [1.07-1.15]	**CeD**	2.28E-02	0.94 [0.89-0.99]
6q25.3	159,470,417	rs212407	*TAGAP*	G	6.74E-14	CeD	1.26E-11	1.13 [1.09-1.18]	RA T1D	1.54E-04	0.95 [0.92-0.97]
7p12.1	51,015,193	rs7780389	*COBL*	T	2.25E-08	**RA**	4.75E-02	1.10 [1.00-1.20]	T1D	2.18E-08	0.71 [0.63-0.80]
10p15.1	6,116,254	rs72776098	*IL2RA*	A	7.10E-10	**SSc**	1.39E-03	1.50 [1.17-1.93]	T1D	2.02E-08	0.61 [0.52-0.73]
10q22.3	81,045,280	rs1250568	*ZMIZ1*	C	3.87E-15	**SSc T1D**	9.04E-03	1.06 [1.01-1.10]	CeD	1.13E-14	0.87 [0.84-0.90]
11q23.3	118,726,843	rs10892299	*DDX6*	T	2.25E-13	**T1D**	2.49E-02	1.07 [1.01-1.13]	CeD **SSc**	2.68E-13	0.87 [0.84-0.90]
12q13.2	56,470,625	rs11171739	*IKZF4*	C	1.87E-20	T1D	1.04E-18	1.23 [1.17-1.28]	RA	3.59E-04	0.93 [0.90-0.97]
15q25.1	79,234,957	rs34593439	*CTSH*	A	1.47E-14	CeD	2.21E-06	1.15 [1.08-1.21]	T1D	1.82E-10	0.77 [0.71-0.83]

Position (bp), base pair position in hg19; **SNP**, single nucleotide polymorphism**; Gene**, annotated gene as described in online methods; **A1**, alternative allele used in the logistic regression; **P2sided,** p-value from the two-sided subset-based meta-analysis; **Pheno risk**, risk (OR>1) disease subset from the subset-based meta-analysis; **Pheno protective**, protective (OR<1) disease subset from the subset-based meta-analysis. Diseases included in the best subset and for which identified associations have not been previously reported are shown in bold

Table S6. Coding variants in tight linkage disequilibrium ($r^2 \geq 0.8$) with lead non-coding polymorphisms according to the European population of the 1000 Genomes Project. All genetic variants were annotated using the variant effect predictor (VEP).

			VEP annotation lead SNP			VEP annotation proxy		
Region	**Position (bp)**	**Lead SNP**	**Consequence**	**Gene symbol**	**Proxy SNP**	**Gene symbol**	**Consequence**	**SIFT**
1p36.32	2,534,978	rs6664969	Intron	*MMEL1*	rs3748816	*MMEL1*	Missense	Tolerated
					rs4648562	*MMEL1*	Synonymous	-
					rs4648658	*MMEL1*	Synonymous	-
					rs4648659	*MMEL1*	Synonymous	-
1p36.13	17,655,407	rs1748041	Intron	*PADI4*	rs1748033	*PADI4*	Synonymous	-
1q32.1	200,875,242	rs12132349	Intron	*C1orf106*	rs296520	*C1orf106*	Missense	Tolerated
7q32.1	128,572,766	rs4731532	Upstream	*IRF5*	rs2004640	*IRF5*	Splice donor	-
11p15.5	2,163,110	rs4244808	Intron	*INS-IGF2*	rs10770125	*IGF2*	Missense	Deleterious
15q25.1	79,234,957	rs34593439	Intron	*CTSH*	rs2289702	*CTSH*	Missense	Deleterious
16p11.2	28,505,660	rs151234	Upstream	*CLN3*	rs151233	*CLN3*	Synonymous	-
16q23.1	75,247,391	rs7202844	Intergenic	-	rs2287990	*CTRB1*	Synonymous	-
22q11.1	21,936,152	rs66534072	Intron	*UBE2L3*	rs2298428	*YJDC*	Missense	Tolerated
22q12.3	37,587,111	rs229533	Upstream	*C1QTNF6*	rs229527	*C1QTNF6*	Missense	Tolerated

Position (bp), base pair position in hg19; **SNP**, single nucleotide polymorphism; **Consequence**: consequence type of this variation on the protein sequence; **Gene symbol**, affected gene; **SIFT**, SIFT prediction if available.

Table S9. Transcription factor binding sites (TFBSs) potentially disrupted by the set of pleiotropic variants. The GenomeRunner web server was used to calculate enrichment p-values using Chi-squared test by evaluating whether the set of common SNPs co-localizes with TFBSs from the ENCODE project more often than expected by chance (see Methods).

TF	P-value	P_{FDR}	Direction
BATF	3.98E-17	6.40E-15	Over
RELA	7.59E-14	6.11E-12	Over
IRF4	3.50E-10	1.88E-08	Over
RUNX3	9.68E-09	3.89E-07	Over
SPI1	8.86E-08	2.38E-06	Over
MTA3	7.41E-08	2.38E-06	Over
POU2F2	1.05E-05	2.41E-04	Over
ATF2	9.72E-05	1.96E-03	Over
ELF1	2.41E-04	4.08E-03	Over
IKZF1	2.53E-04	4.08E-03	Over
USF2	4.17E-04	6.10E-03	Over
TAF1	1.79E-03	2.40E-02	Over

TF, transcription factor; $\mathbf{P_{FDR}}$, p-value after multiple testing correction using the Benjamini–Hochberg false discovery rate (FDR) procedure; **Direction**, direction of the enrichment. Over denotes overrepresentation of regulatory elements.

Table S10. Biological pathways significantly enriched among the set of common genes. KEGG pathway analysis was performed using WebGestalt (WEB-based GEne SeT AnaLysis Toolkit) with the human genome as the reference set, the Benjamini Hochberg adjustment for multiple testing, and a minimum number of 2 genes per category.

KEEG pathway	Genes	Enrichment statistics
Th1 and Th2 cell differentiation	*GATA3, RBPJ, IL2RA, IL12A, PRKCQ, STAT4, TYK2*	C=92; O=7; E=0.24; R=28.73; P-value=2.01e-09; FDR=6.21e-07
Measles	*IL2RA, FASLG, IL12A, PRKCQ, TNFAIP3, TYK2, CD28*	C=136; O=7; E=0.36; R=19.44; P-Value=3.14e-08; FDR=4.85e-06
Jak-STAT signaling pathway	*IL2RA, IL12A, PTPN2, STAT4, TYK2*	C=158; O=5; E=0.42; R=11.95; P-value=4.4e-05; FDR=4.53e-03
Allograft rejection	*FASLG, IL12A, CD28*	C=38; O=3; E=0.1; R=29.81; P-value=1.25e-04; FDR=7.85e-03
T cell receptor signaling pathway	*RASGRP1, CTLA4, PRKCQ, CD28*	C=105; O=4; E=0.28; R=14.39; P-value=1.42e-04; FDR=7.85e-03
Th17 cell differentiation	*GATA3, IL2RA, PRKCQ, TYK2*	C=107; O=4; E=0.28; R=14.12; P-value=1.53e-04; FDR=7.85e-03
Type I diabetes mellitus	*FASLG, IL12A, CD28*	C=43; O=3; E=0.11; R=26.35; P-value=1.82e-04; FDR=8.02e-03
Autoimmune thyroid disease	*CTLA4, FASLG, CD28*	C=53; O=3; E=0.14; R=21.38; P-value=3.39e-04; FDR=1.31e-02
Inflammatory bowel disease (IBD)	*GATA3, IL12A, STAT4*	C=65; O=3; E=0.17; R=17.43; P-value=6.2e-04; FDR=2.13e-02

C, the number of reference genes in the category; **O**, the number of genes in the user gene list and also in the category; **E**, the expected number in the category; **R**, ratio of enrichment; **P-value**, p value from hypergeometric test; **FDR**, p-value after multiple testing correction using the Benjamini–Hochberg false discovery rate (FDR) procedure.

Supplemental Figures

Figure S1. Quantile–quantile plots for the p-values of each individual disease, celiac disease (a), rheumatoid arthritis (b), systemic sclerosis (c), and type 1 diabetes (d), and the cross disease meta-analysis (e). The x-axis indicates the expected distribution of -log10 (P values) and the y-axis indicates the observed distribution of -log10 (P values). Genomic inflation of the observed distribution is indicated by λ and λ_{1000}.

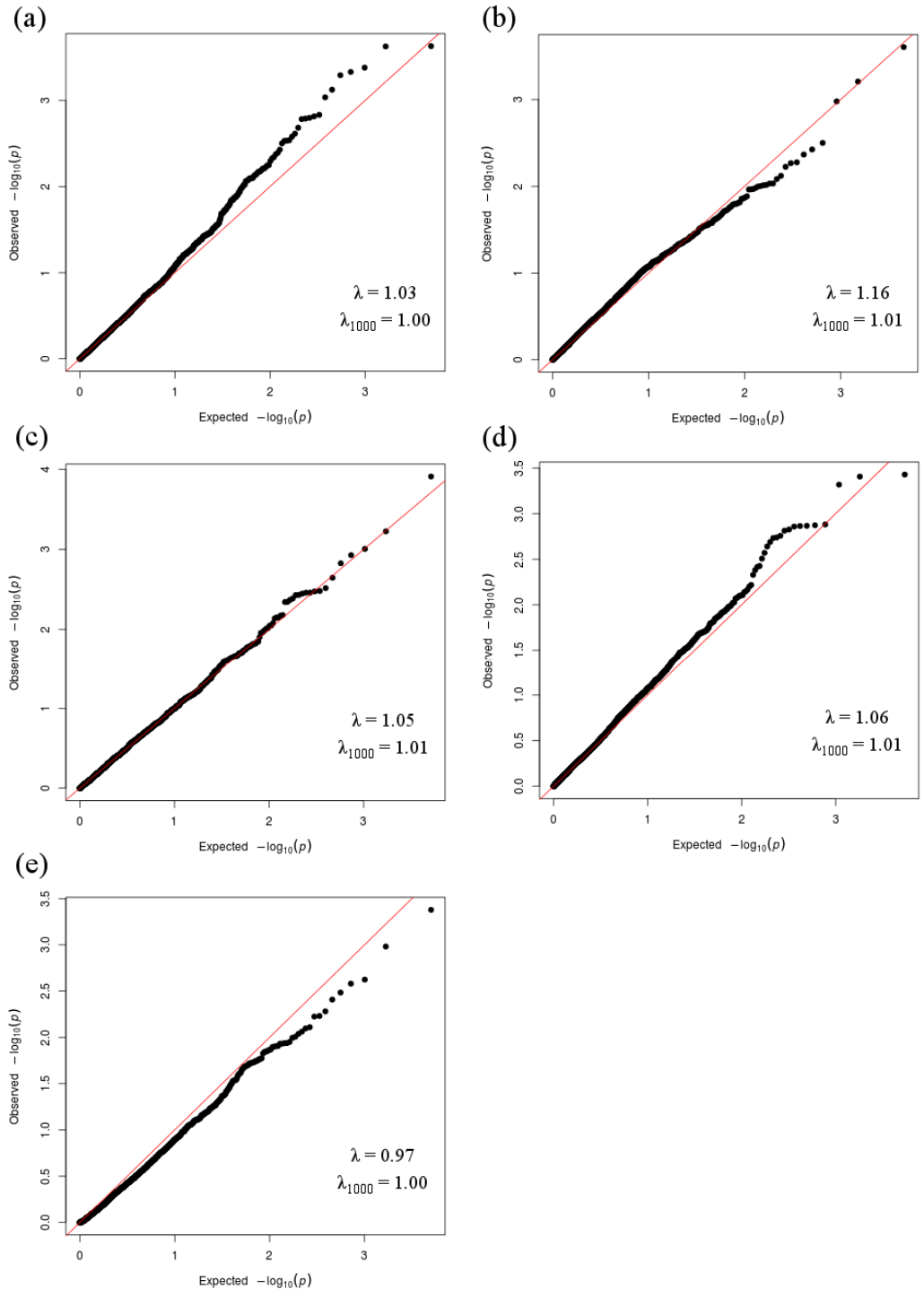


Figure S2. Empirical −log10(P)-distribution of the Zmax statistic obtained by simulating 300 × 10^6 replicates of four normally distributed random variables.

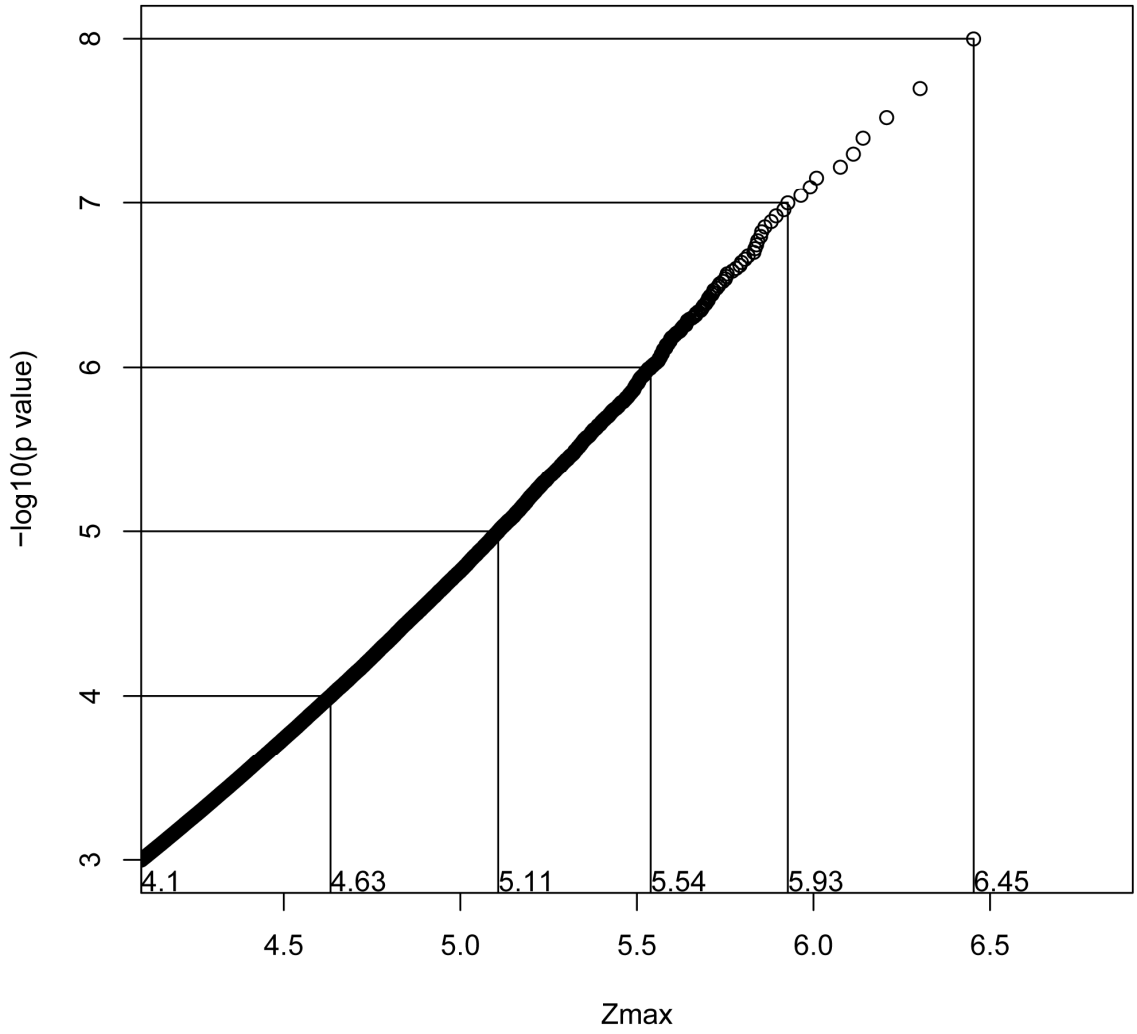


Figure S3. Manhattan plot of the subset-based meta-analysis of Immunochip data from celiac disease (CeD), systemic sclerosis (SSc), rheumatoid arthritis (RA) and type 1 diabetes (T1D). After applying quality control filters and imputation (see methods), we analyzed 252,970 polymorphisms in 37,159 autoimmune-disease patients and 22,308 healthy controls. The -log10 of the subset-based meta-analysis p-values are plotted against their physical chromosomal position. The red line represents the genome-wide level of significance ($p = 5x10^{-8}$).

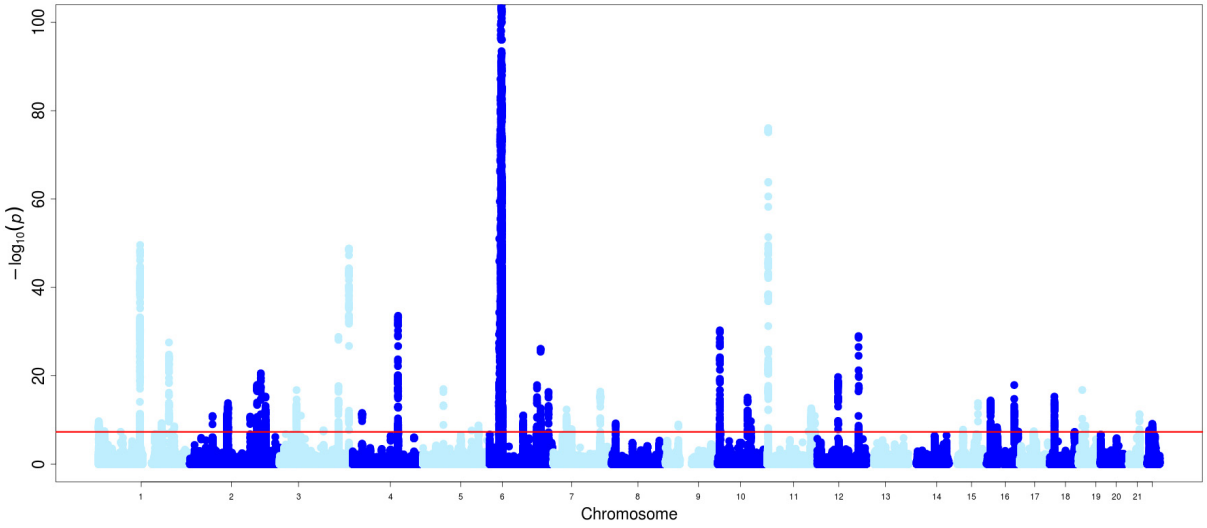


Figure S4. Disease-specific odds ratio for the pleiotropic variants showing opposite allelic effects across autoimmune diseases. Circles represent the analyzed diseases (red: celiac disease; yellow: rheumatoid arthritis; green: systemic sclerosis; blue: type 1 diabetes). Large circles denote diseases contributing to the association signal (i.e. included in the best subset).

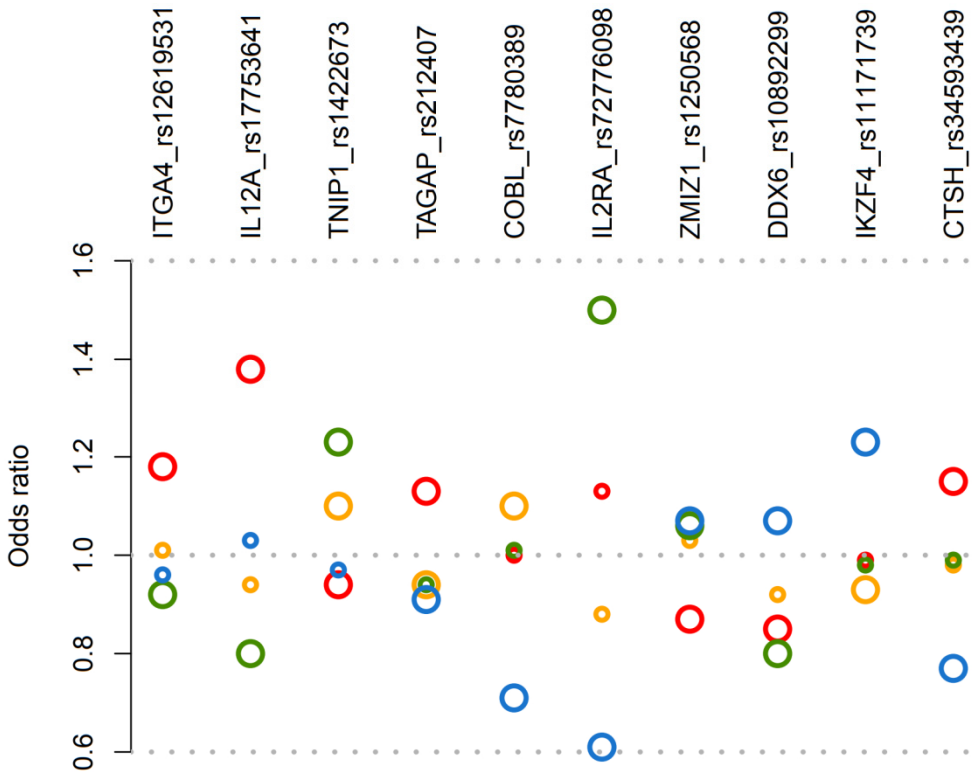


Figure S5. Regional association plots of the novel genome-wide associated locus for rheumatoid arthritis (RA), 2q32.3. (a) Results of the RA meta-analysis for the 2q32.3 region. Negative log10-tranformed p-value is shown for SNPs in the regions flanking 500 kb on either side of the index SNP (purple diamond). Both the most significance SNP within the region (index SNP) and the new genome-wide associated variant (rs10931468) are indicated in the plot. The index SNP is shown as a diamond and the r^2 values of the remaining SNPs are indicated by color (see legend). (b) Results of the RA meta-analysis for the 2q32.3 region after conditioning for the most associated SNP (rs7582694). The genes within the region are annotated and indicated by arrows. Plots were generated using LocusZoom (http://locuszoom.org/).

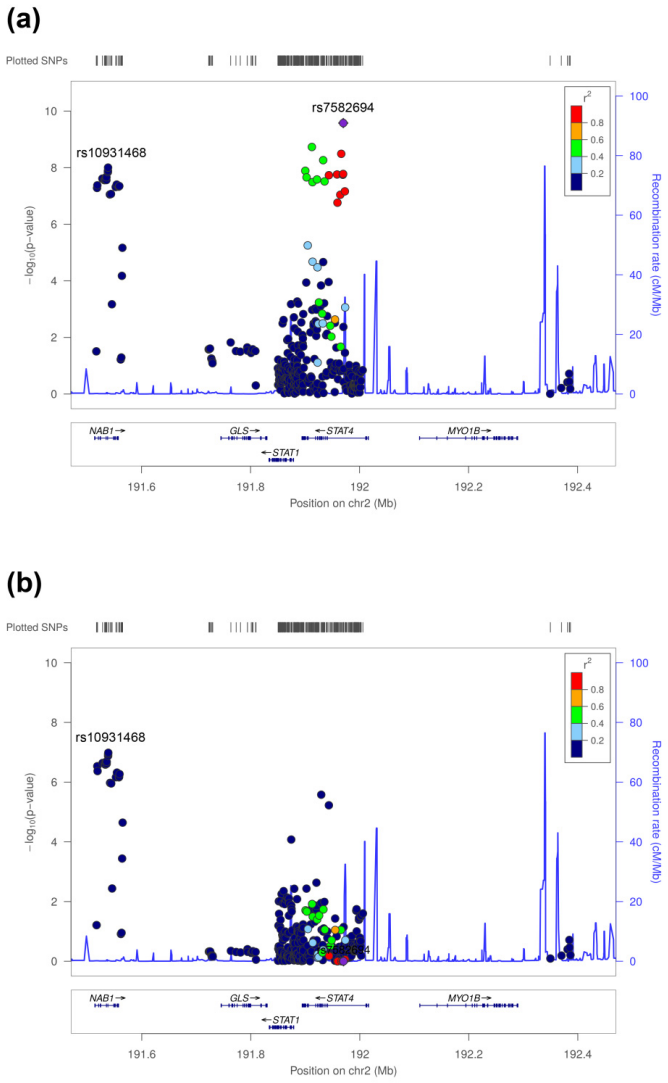
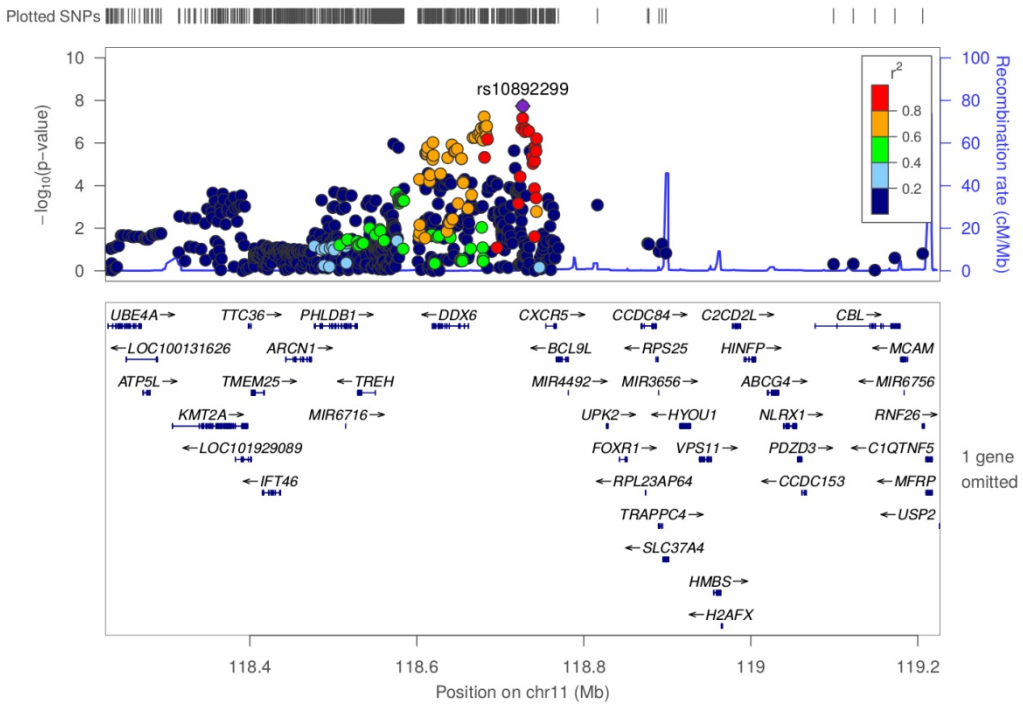
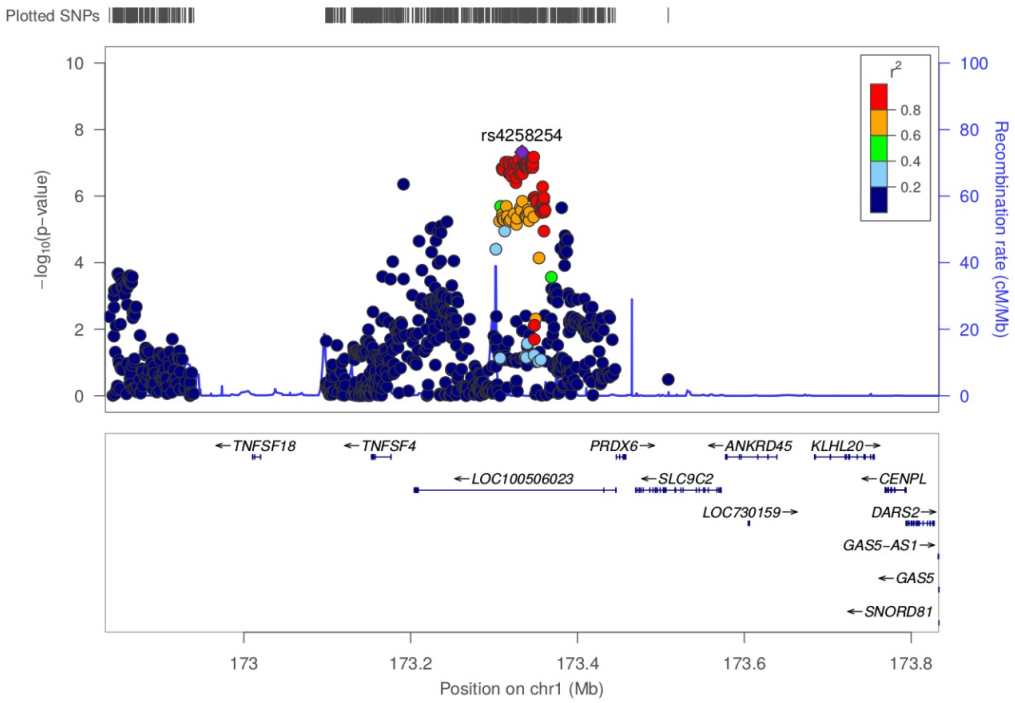


Figure S6. Regional association plots of the novel genome-wide associated loci for systemic sclerosis (SSc), 11q23.3 (a), 1q25.1 (b), and 1q25.3 (c). Results of the SSc meta-analysis (−log10 P) are shown for SNPs in the regions flanking 500 kb on either side of the index SNPs (purple diamonds). The index SNPs are shown as diamonds and the r^2 values of the remaining SNPs are indicated by color (see legend). The genes within the region are annotated and indicated by arrows. Plots were generated using LocusZoom (http://locuszoom.org/).

(a)



(b)


Plotted SNPs
rs4258254
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
TNFSF18
TNFSF4
PRDX6
ANKRD45
KLHL20
LOC100506023
SLC9C2
CENPL
LOC730159
DARS2
GAS5-AS1
GAS5
SNORD81
Position on chr1 (Mb)

(c)

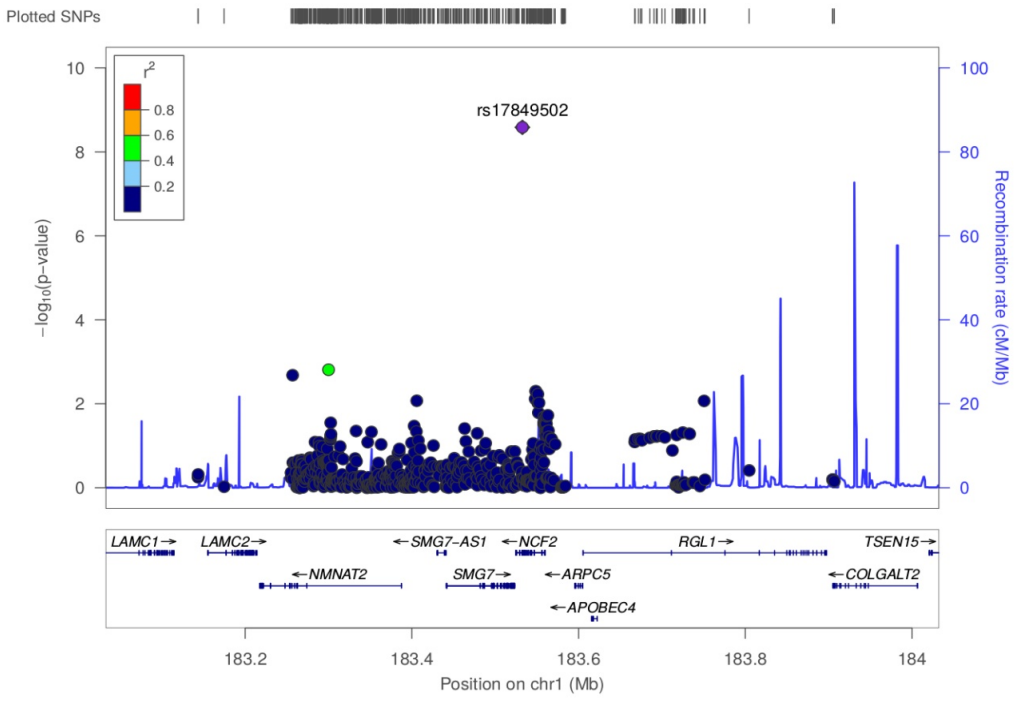

Plotted SNPs
rs17849502
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
LAMC1
LAMC2
SMG7-AS1
NCF2
RGL1
TSEN15
NMNAT2
SMG7
ARPC5
COLGALT2
APOBEC4
Position on chr1 (Mb)

Figure S7. Regional association plot of the novel genome-wide associated locus for celiac disease (CeD), 3p14.1. Results of the CeD meta-analysis (−log10 P) are shown for SNPs in the region flanking 500 kb on either side of the index SNP. The index SNP is shown as a diamond and the r^2 values of the remaining SNPs are indicated by color (see legend). The genes within the region are annotated and indicated by arrows. Plot was generated using LocusZoom (http://locuszoom.org/).

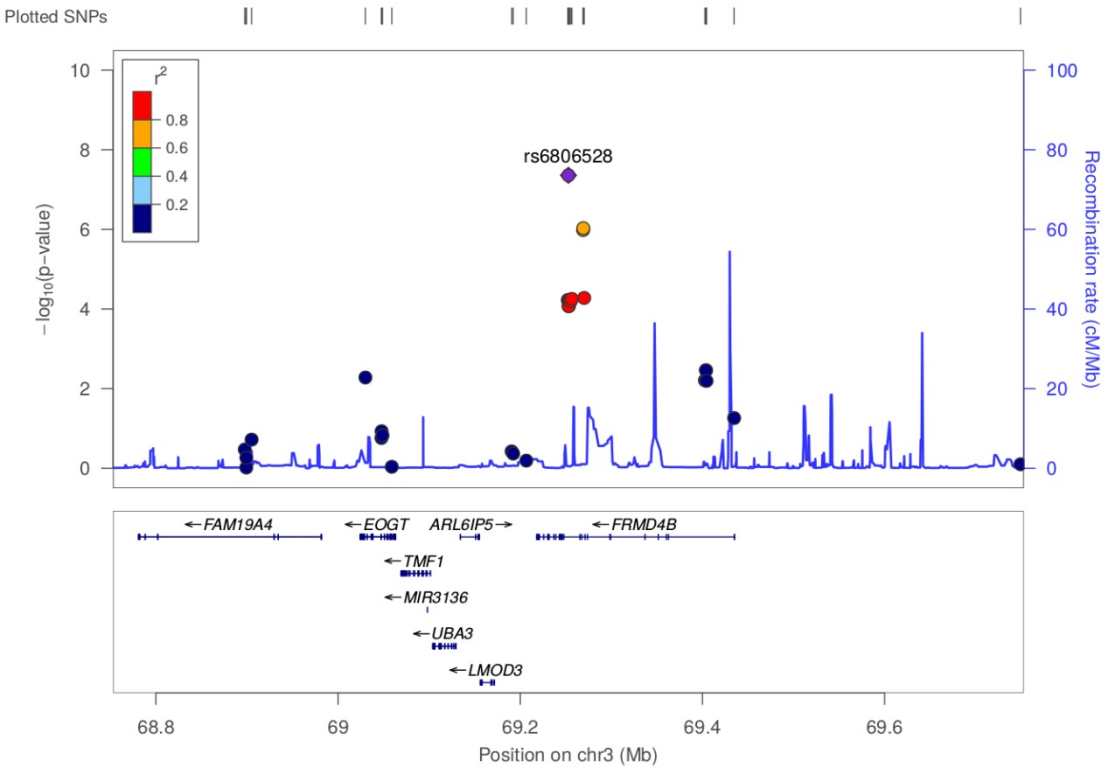
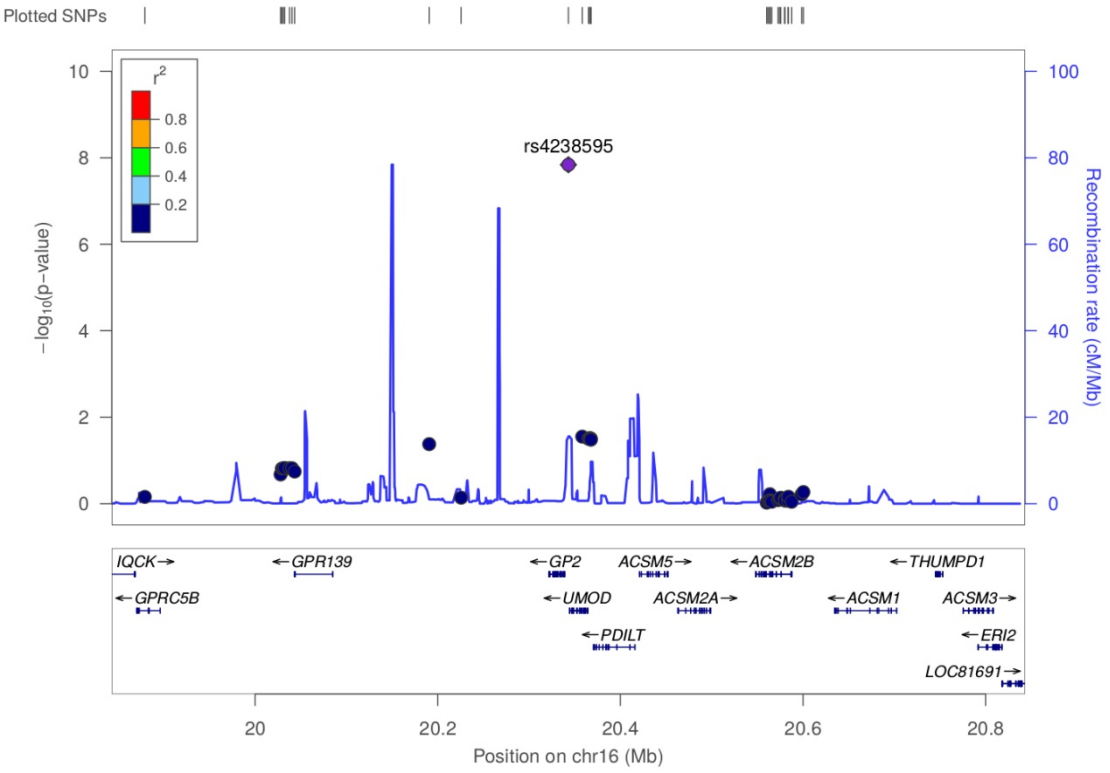


Figure S8. Regional association plot of the novel genome-wide associated locus for type 1 diabetes (T1D), 16p12.3. Results of the T1D analysis (−log10 P) are shown for SNPs in the regions flanking 500 kb on either side of the index SNP (purple diamond). The index SNP is shown as a diamond and the r^2 values of the remaining SNPs are indicated by color (see legend). The genes within the region are annotated and indicated by arrows. Plots were generated using LocusZoom (http://locuszoom.org/).



Supplemental Note

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