Additional file 1: supplementary figures and tables

Table S1. Summary data from all GWAS used in current study

Disease	Abbreviation	Cases	Controls	Ethnics	SNPs	Reference
Amyotrophic lateral sclerosis	ALS	20,806	59,804	EUR	10,031,417	17
Amyotrophic lateral sclerosis	ALS replication	14,387	27,008	EUR & EAS	6,613,543	26
asthma	asthma	10,549	47,146	EUR	33,771,858	18
Celiac disease	CeD	4,533	10,750	EUR	523,398	24
Crohn's disease	CD	12,194	28,072	EUR	9,570,787	25
inflammatory bowel disease	IBD	25,042	34,915	EUR	7,345,446	25
multiple sclerosis	MS	33,647	449,056	EUR	17,510,617	19
psoriasis	psoriasis	17,008	37,154	EUR	7,055,881	20
rheumatoid arthritis	RA	29,880	73,758	EUR & EAS	9,739,303	21
systemic lupus erythematosus	SLE	7,219	15,991	EUR	7,915,251	22
type 1 diabetes	T1D	9,934	16,956	EUR	2,060,920	23
ulcerative colitis	UC	12,366	33,609	EUR	9,588,016	25
Parkinson's disease	PD	33,674	449,056	EUR	17,510,617	36
Alzheimer's disease	AD	17,008	37,154	EUR	7,055,881	37

EUR, European; EAS, East Asian; SNP, single nucleotide polymorphism; GWAS, genome-wide association study; 23andMe contributions were excluded in the PD GWAS, as described in the original publication.

Table S2. Genetic correlation between AD, ALS, PD and autoimmune disorders

	AD	ALS	PD
asthma	0.04 (0.45)	0.08 (0.23)	-0.10 (0.01)
CeD	-0.03 (0.54)	**0.58 (5.82E-28)**	0.05 (0.24)
CD	-0.02 (0.48)	**-0.25 (2.75E-10)**	0.00 (0.88)
IBD	-0.02 (0.55)	**-0.33 (1.16E-16)**	-0.02 (0.41)
MS	0.05 (0.18)	**0.23 (1.11E-08)**	0.02 (0.62)
psoriasis	0.07 (0.29)	-2.86E-03 (0.97)	-0.02 (0.82)
RA	0.03 (0.53)	**0.22 (6.17E-07)**	**-0.10 (3.31E-03)**
SLE	0.03 (0.36)	**0.26 (6.58E-07)**	0.04 (0.26)
UC	-0.01 (0.68)	**-0.32 (1.96E-13)**	-0.06 (0.09)

Values are presented as genetic correlation (P value). Values in bold denote significant correlation. Genetic correlation for T1D was not estimated since beta value was not available in the original GWAS.

Table S3. Risk loci associated with ALS conditional on autoimmune diseases

SNP	Genomic position (GRCh37)	Closest gene	FDR value	Original ALS P value	Replication ALS P value
rs72714928	1:161207232	*NR1I3*	5.20E-03	2.12E-06	4.29E-04
rs1004197	1:94249540	*BCAR3*	3.36E-03	1.22E-06	2.83E-02
rs61527579	2:76237892	*GCFC2*	5.27E-03	2.67E-06	1.22E-03
rs3828599	5:150401796	*GPX3*	3.26E-05	8.08E-08	1.22E-07
rs10463311	5:150410835	*TNIP1*	1.72E-04	4.00E-08	1.32E-08
rs538622	5:172347679	*ERGIC1*	2.00E-03	6.69E-07	1.22E-04
rs7805982	7:42429859	*GLI3*	6.56E-03	2.86E-06	2.35E-04
rs17070492	8:2420855	*LOC101927815*	5.33E-04	1.04E-07	3.27E-07
rs9969832	9:27493063	*MOB3B*	3.39E-24	2.01E-28	5.03E-21
rs2484319	9:27563755	*C9orf72*	1.86E-24	1.27E-29	5.74E-23
rs11195948	10:114163515	*ACSL5*	2.26E-03	9.14E-07	4.04E-05
rs61880881	11:22270782	*ANO5*	2.25E-03	2.73E-06	n.a.
rs653178	12:112007756	*ATXN2*	6.73E-03	5.18E-04	n.a.
rs118082508	12:57318819	*SDR9C7*	1.60E-04	1.97E-08	n.a.
rs113247976	12:57975700	*KIF5A*	2.60E-06	6.43E-10	n.a.
rs12320537	12:58021091	*B4GALNT1*	5.74E-03	6.97E-06	7.59E-02
rs116900480	12:58656105	*LINC02403*	5.34E-06	6.60E-10	n.a.
rs12308116	12:64710719	*C12orf56*	6.50E-03	4.32E-06	6.11E-07
rs41292019	12:64849716	*TBK1*	8.12E-05	8.39E-09	n.a.
rs447614	14:31080799	*G2E3*	1.24E-03	1.74E-07	3.96E-07
rs1950882	14:31172253	*SCFD1*	1.22E-03	1.69E-07	7.69E-07
rs2295172	14:92492651	*TRIP11*	2.65E-03	8.91E-07	1.38E-04
rs1107115	14:92546544	*ATXN3*	1.93E-03	6.47E-07	4.38E-05
rs62029863	16:50749408	*NOD2*	7.12E-04	7.91E-05	n.a.
rs34517613	17:26610252	*KRT18P55*	5.31E-03	2.18E-06	n.a.
rs35714695	17:26719788	*SARM1*	8.25E-03	2.89E-06	3.07E-10
rs2285642	17:34912744	*GGNBP2*	4.52E-03	1.80E-06	1.18E-06
rs12608932	19:17752689	*UNC13A*	3.86E-11	6.35E-15	2.70E-10
rs56185963	20:48514826	*SLC9A8*	8.34E-03	8.96E-06	4.53E-04
rs112572132	20:48533630	*LOC105372653*	5.35E-03	6.50E-06	4.40E-04
rs75087725	21:45753117	*CFAP410*	2.17E-10	1.85E-14	n.a.
rs62241220	22:50747507	*DENND6B*	7.37E-03	7.45E-06	n.a.

n.a., not available; SNP, single nucleotide polymorphism; FDR, false discovery rate.

Table S4. eQTL revealing functional effects of shared risk SNPs in tissues from GTEx

Gene	Tissue	Genomic position (GRCh37)	SNP	Nominal P value
ATXN3	Brain_Cerebellum	14:92495536	rs2896190	2.14E-08
ATXN3	Muscle_Skeletal	14:92541852	rs7152876	1.25E-10
C9orf72	Brain_Nucleus_accumbens_basal_ganglia	9:27559835	rs774357	2.71E-08
C9orf72	Brain_Spinal_cord_cervical_c-1	9:27516640	rs774351	7.62E-07
C9orf72	Muscle_Skeletal	9:27516640	rs774351	7.63E-08
DENND6B	Brain_Cortex	22:50748930	rs68069258	5.06E-10
DENND6B	Brain_Frontal_Cortex_BA9	22:50742935	rs34544325	8.60E-10
DENND6B	Whole_Blood	22:50742611	rs62241211	3.33E-08
DHRS11	Brain_Cerebellum	17:34951204	rs2285640	2.54E-07
DHRS11	Brain_Cortex	17:34937221	rs9903355	1.31E-09
DHRS11	Brain_Frontal_Cortex_BA9	17:34937221	rs9903355	8.11E-07
DHRS11	Brain_Nucleus_accumbens_basal_ganglia	17:34951204	rs2285640	9.76E-09
DHRS11	Muscle_Skeletal	17:34951204	rs2285640	2.74E-10
GGNBP2	Brain_Caudate_basal_ganglia	17:34937221	rs9903355	7.94E-08
GGNBP2	Muscle_Skeletal	17:34951204	rs2285640	3.60E-14
GGNBP2	Whole_Blood	17:34951204	rs2285640	5.64E-11
MYO19	Muscle_Skeletal	17:34951204	rs2285640	1.64E-21
MYO19	Whole_Blood	17:34951204	rs2285640	7.15E-09
NOD2	Whole_Blood	16:50730229	rs2066850	7.84E-11
PLXNB2	Muscle_Skeletal	22:50742935	rs34544325	5.05E-21
PPP6R2	Muscle_Skeletal	22:50747507	rs62241220	9.39E-16
SCFD1	Brain_Anterior_cingulate_cortex_BA24	14:31183168	rs6571361	2.03E-07
SCFD1	Brain_Cerebellar_Hemisphere	14:31059969	rs7154847	2.52E-08
SCFD1	Brain_Cerebellum	14:31183168	rs6571361	1.25E-12
SCFD1	Muscle_Skeletal	14:31080800	rs447853	1.70E-11
SCFD1	Whole_Blood	14:31183168	rs6571361	2.36E-25
SLC9A8	Brain_Cerebellar_Hemisphere	20:48578734	rs113558364	1.36E-10
SLC9A8	Brain_Cerebellum	20:48561156	rs4810992	3.10E-08
SLC9A8	Muscle_Skeletal	20:48561156	rs4810992	9.97E-13
TMEM116	Whole_Blood	12:111989979	rs848132	4.42E-07
TRIP11	Brain_Cerebellum	14:92496613	rs4556729	4.48E-07
TRIP11	Muscle_Skeletal	14:92497990	rs10138217	3.96E-18
ZNHIT3	Whole_Blood	17:34937221	rs9903355	8.23E-15

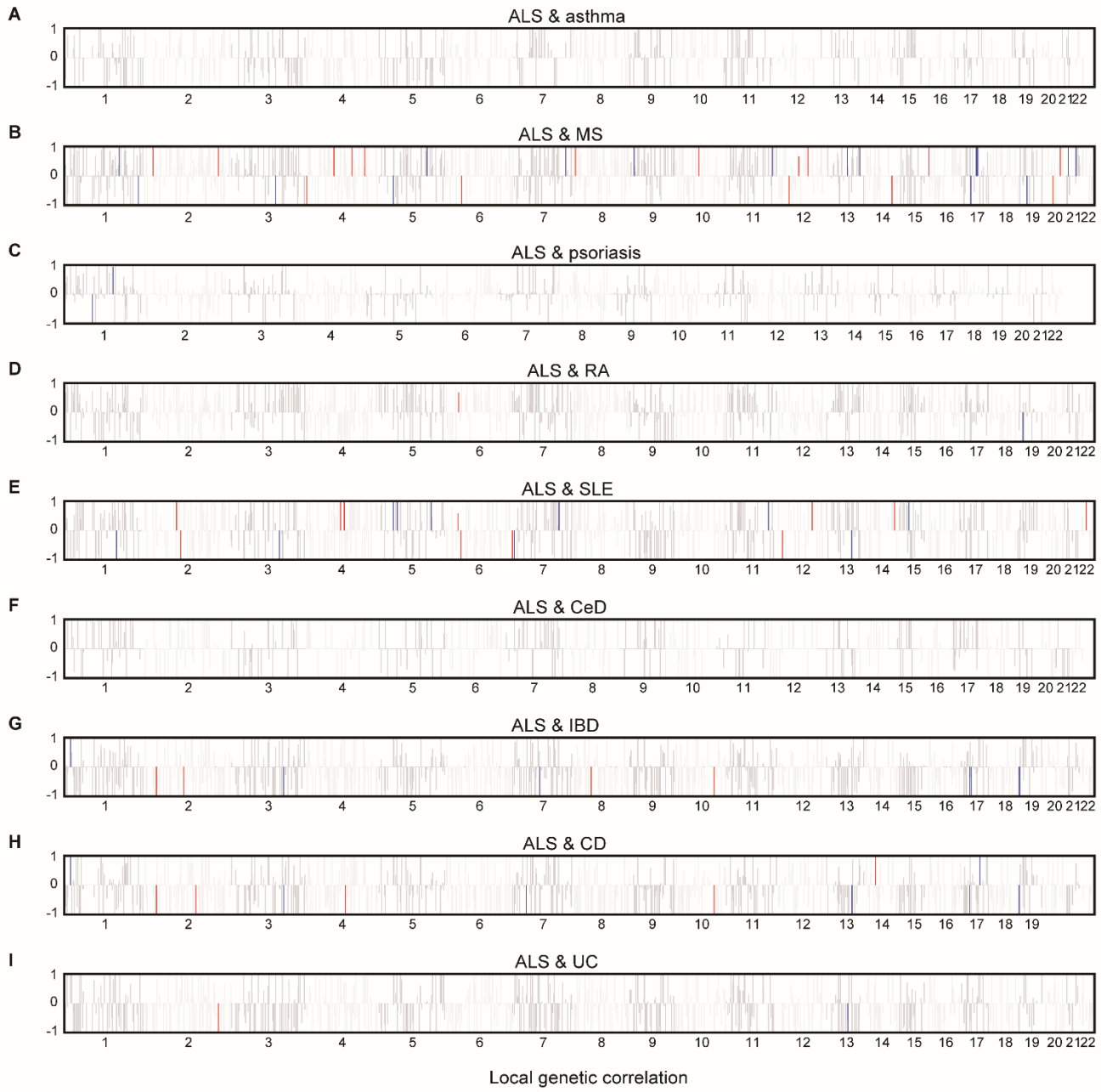
cis-eQTL with the most significant nominal P value for each gene in target tissues were listed

Table S5. Functional annotation of shared risk genes

GO ID		P value	FDR adjusted P value
GO:0097517	contractile actin filament bundle	1.26E-03	0.00378
GO:0032432	actin filament bundle	1.57E-03	0.0127
GO:0005801	cis-Golgi network	1.61E-03	0.0127
GO:0042641	actomyosin	1.81E-03	0.0127
GO:0047485	protein N-terminus binding	3.94E-03	0.0473
GO:0015629	actin cytoskeleton	8.58E-03	0.0129

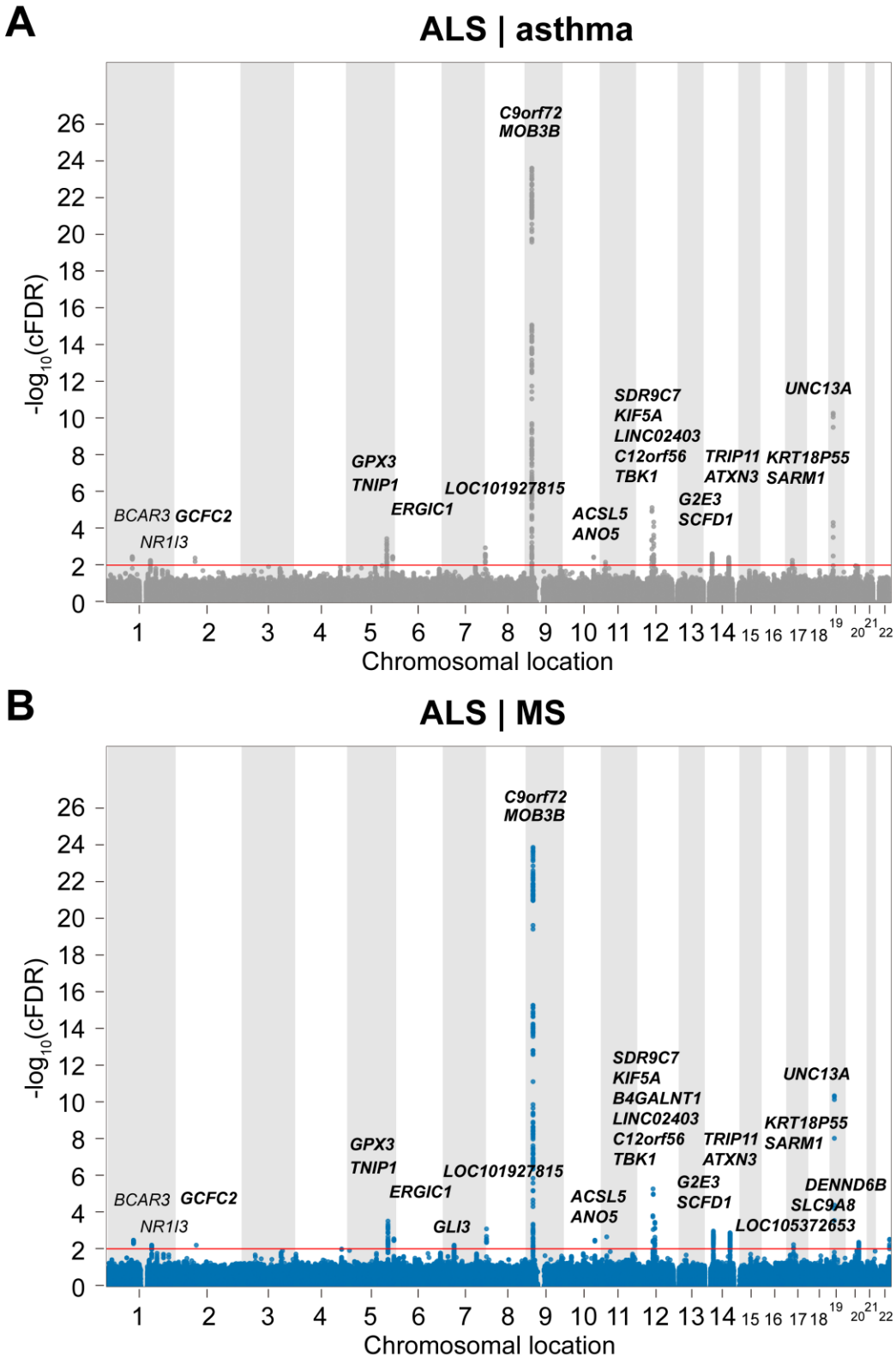
GO, Gene Ontology; FDR, false discovery rate.

Figure S1. Manhattan-style plots showing the estimates of local genetic correlation between ALS and autoimmune disorders



No regions with significant local genetic correlation were identified after Bonferroni correction. Regions with nominally significant correlation (P <0.05) were shown as blue (odd chromosome) and red (even chromosome) lines. Y axis denotes the genetic correlation. Plots were generated using ρ-HESS with default parameters. The figure is suggested to view online for higher resolution.

Figure S2. Conditional Manhattan plots showing risk loci for ALS conditional on each autoimmune disease



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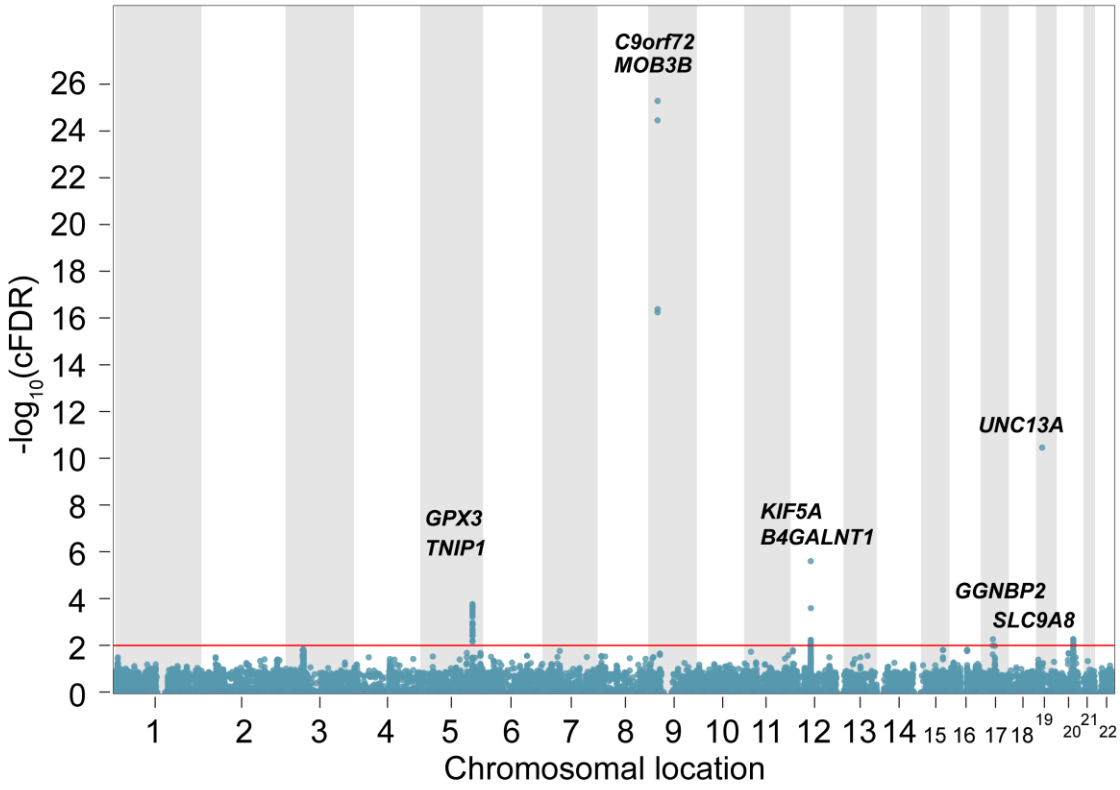
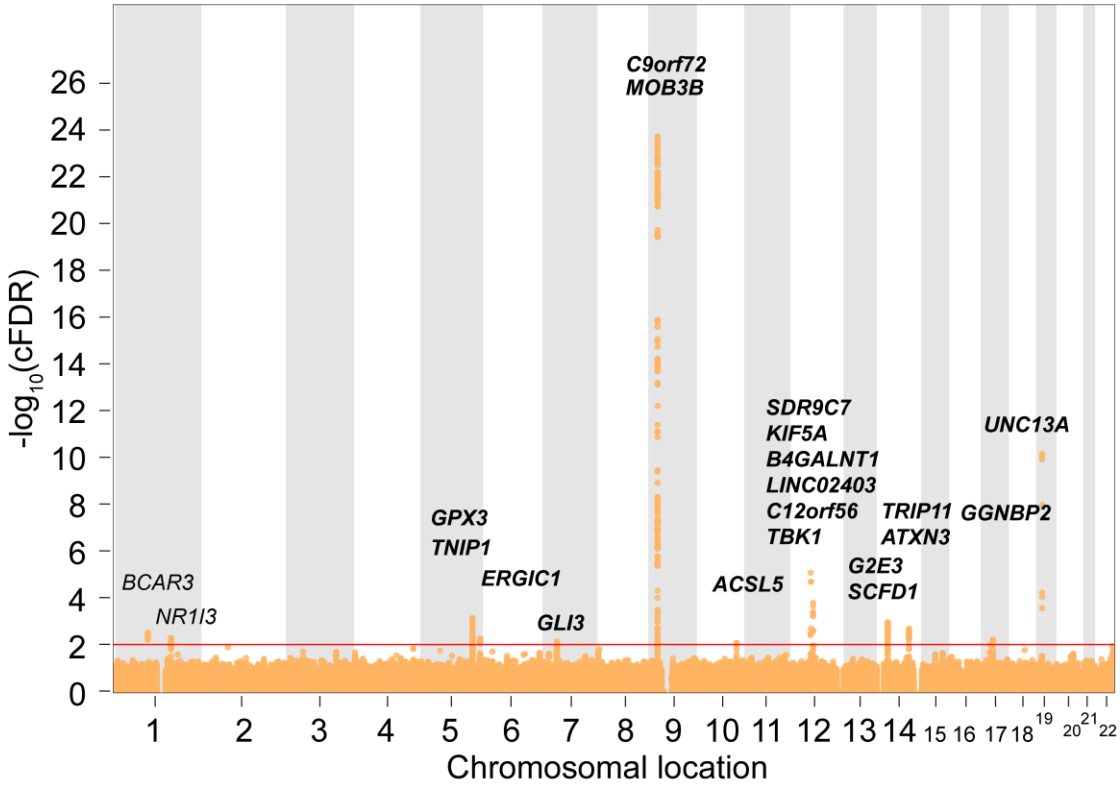
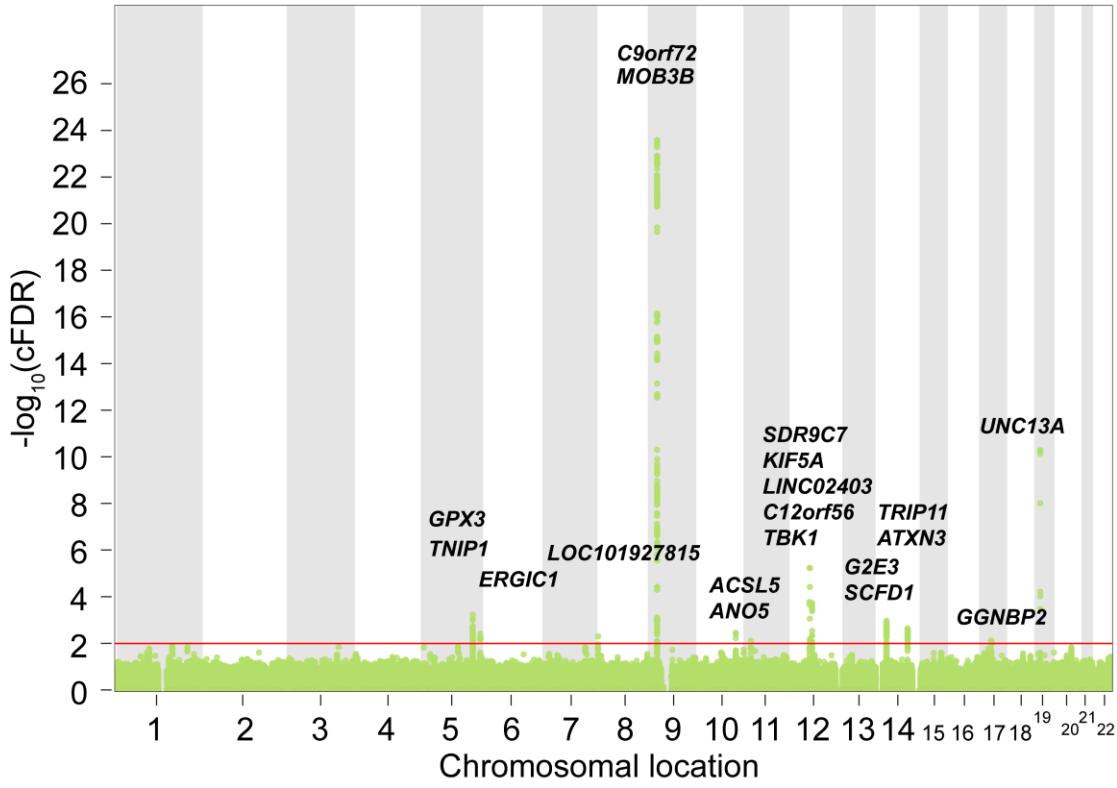

ALS | psoriasis
C9orf72
MOB3B
UNC13A
GPX3
TNIP1
KIF5A
B4GALNT1
GGNBP2
SLC9A8
-log10(cFDR)
Chromosomal location

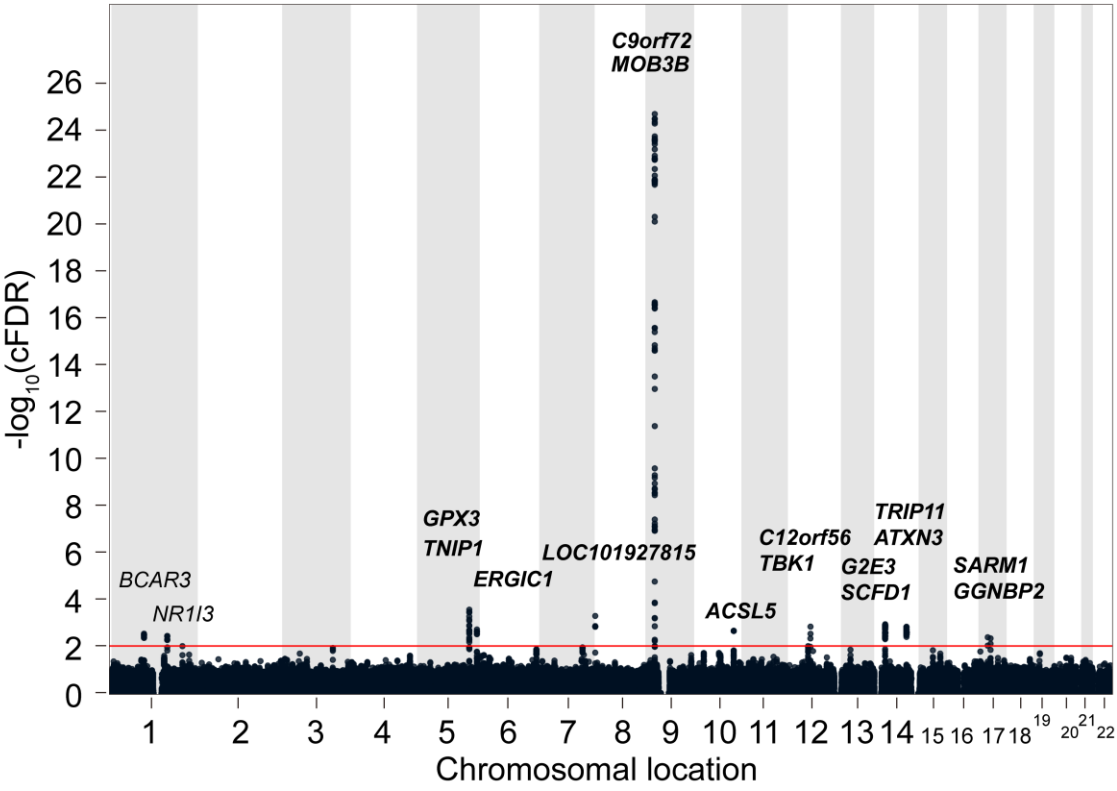
D


ALS | RA
C9orf72
MOB3B
SDR9C7
KIF5A
B4GALNT1
LINC02403
C12orf56
TBK1
TRIP11
ATXN3
G2E3
SCFD1
UNC13A
GGNBP2
GPX3
TNIP1
ERGIC1
GLI3
ACSL5
BCAR3
NR1I3
-log10(cFDR)
Chromosomal location

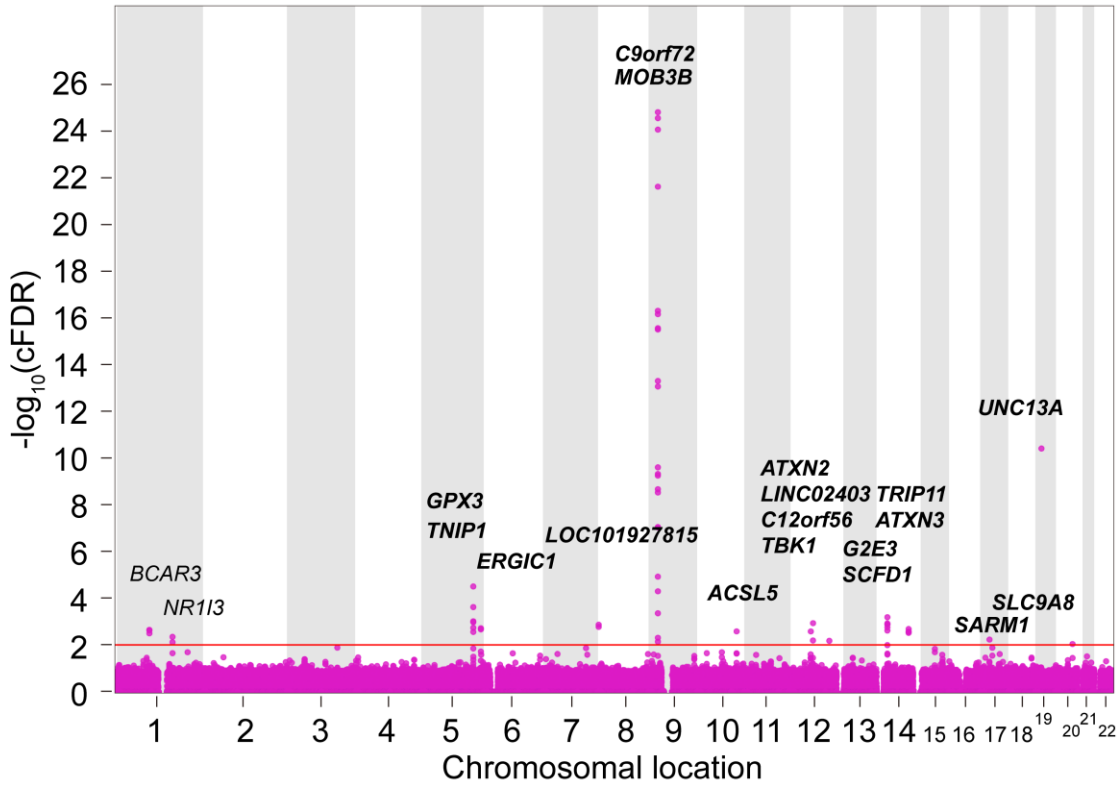
E


ALS | SLE
C9orf72
MOB3B
SDR9C7
KIF5A
LINC02403
C12orf56
TBK1
TRIP11
ATXN3
G2E3
SCFD1
UNC13A
GPX3
TNIP1
ERGIC1
LOC101927815
ACSL5
ANO5
GGNBP2
-log10(cFDR)
Chromosomal location

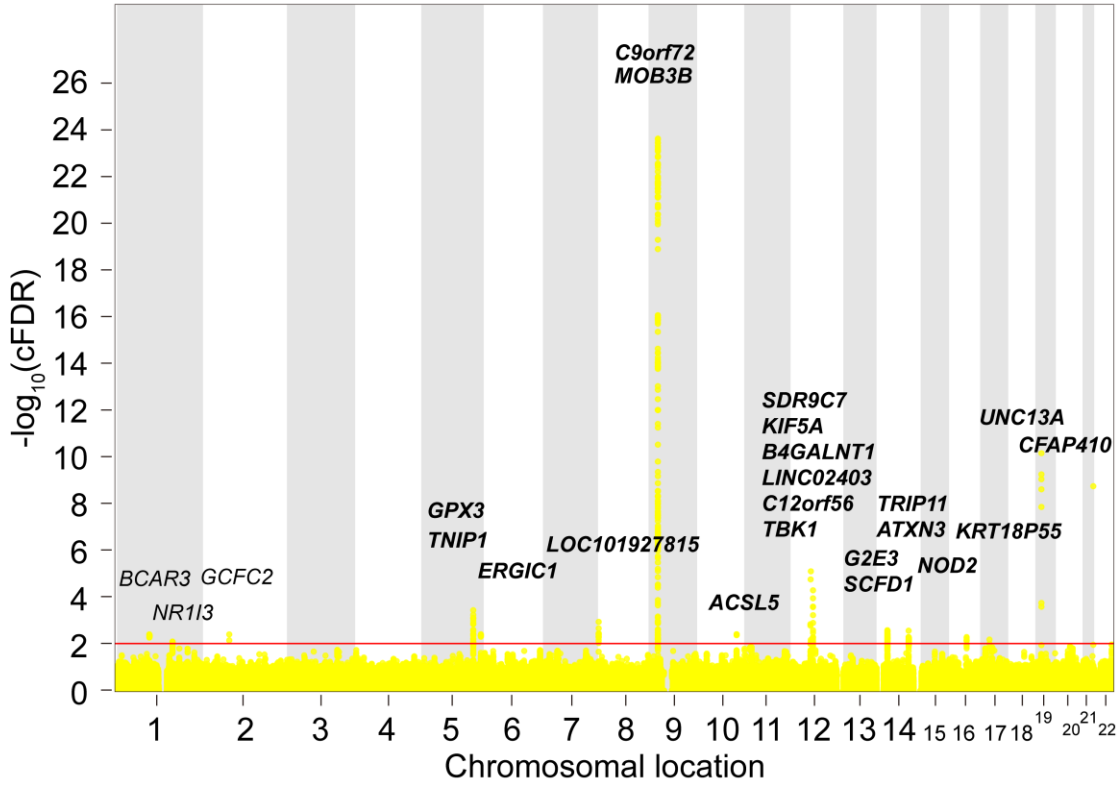
F


ALS | T1D
C9orf72
MOB3B
GPX3
TNIP1
ERGIC1
LOC101927815
BCAR3
NR1I3
ACSL5
C12orf56
TBK1
TRIP11
ATXN3
G2E3
SCFD1
SARM1
GGNBP2
-log10(cFDR)
Chromosomal location

G


ALS | CeD
C9orf72
MOB3B
UNC13A
ATXN2
LINC02403
TRIP11
C12orf56
ATXN3
TBK1
G2E3
SCFD1
GPX3
TNIP1
LOC101927815
ERGIC1
ACSL5
BCAR3
NR1I3
SLC9A8
SARM1
-log10(cFDR)
Chromosomal location

H


ALS | IBD
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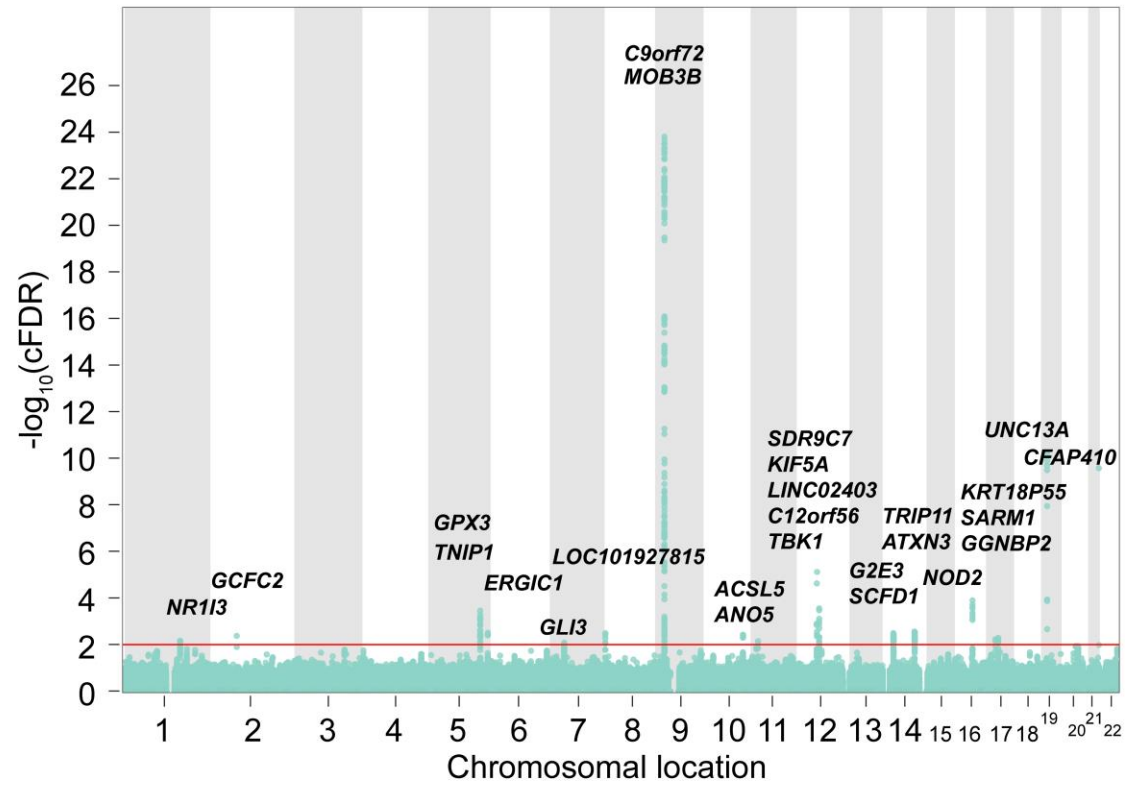
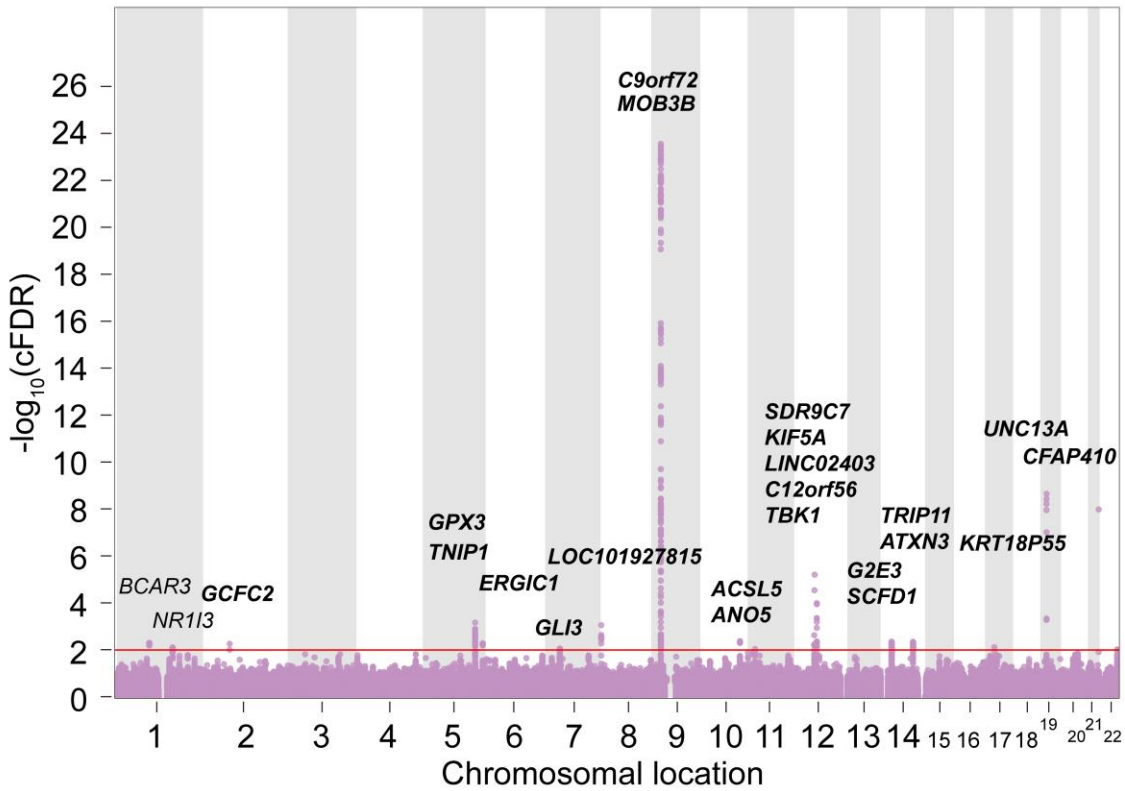
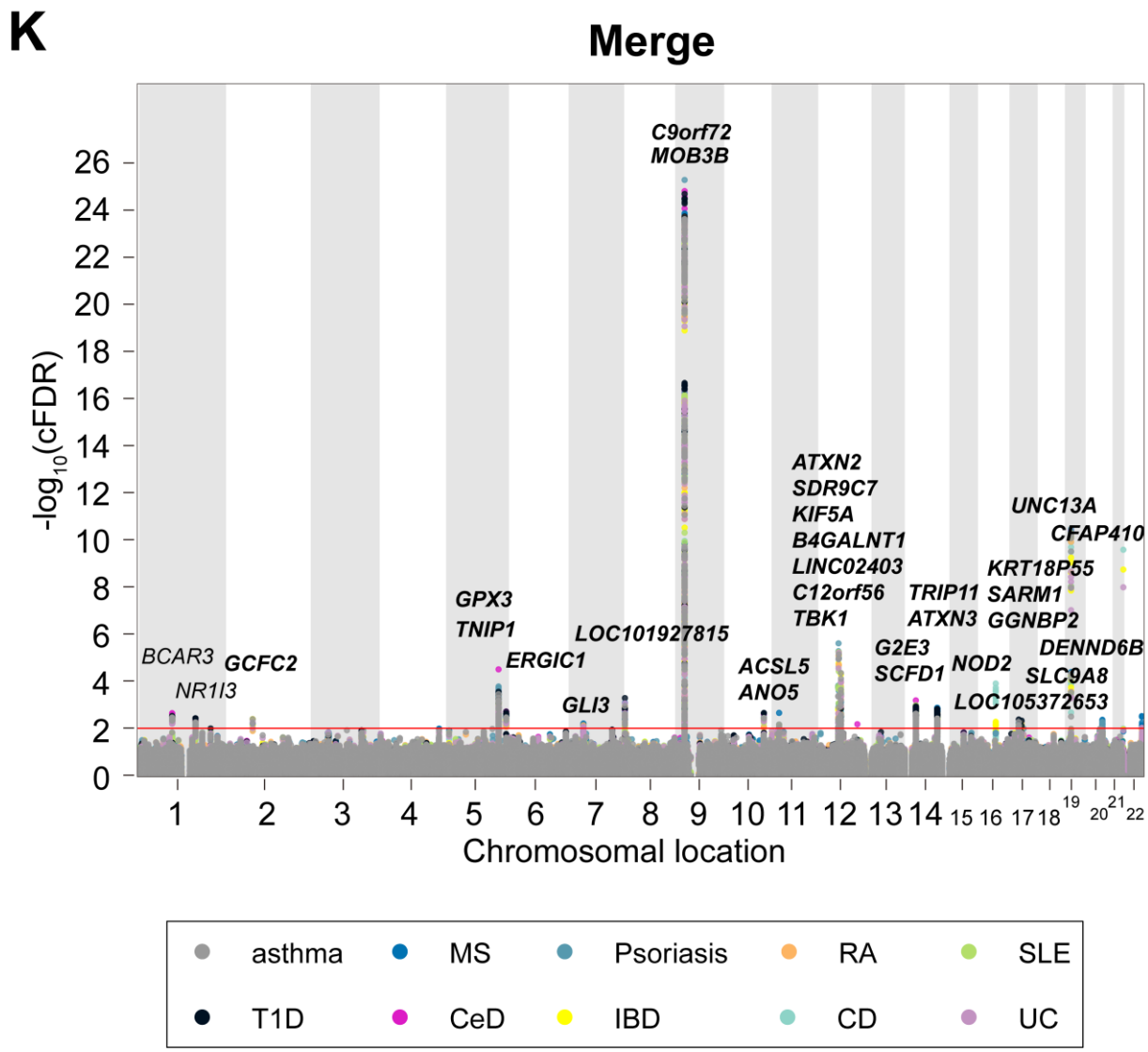
MOB3B
SDR9C7
KIF5A
B4GALNT1
LINC02403
C12orf56
TBK1
UNC13A
CFAP410
TRIP11
ATXN3
KRT18P55
G2E3
SCFD1
NOD2
GPX3
TNIP1
LOC101927815
ERGIC1
ACSL5
BCAR3
GCFC2
NR1I3
-log10(cFDR)
Chromosomal location

I


ALS | CD
-log10(cFDR)
Chromosomal location
C9orf72
MOB3B
GPX3
TNIP1
ERGIC1
LOC101927815
GLI3
GCFC2
NR1I3
ACSL5
ANO5
SDR9C7
KIF5A
LINC02403
C12orf56
TBK1
G2E3
SCFD1
TRIP11
ATXN3
NOD2
UNC13A
CFAP410
KRT18P55
SARM1
GGNBP2

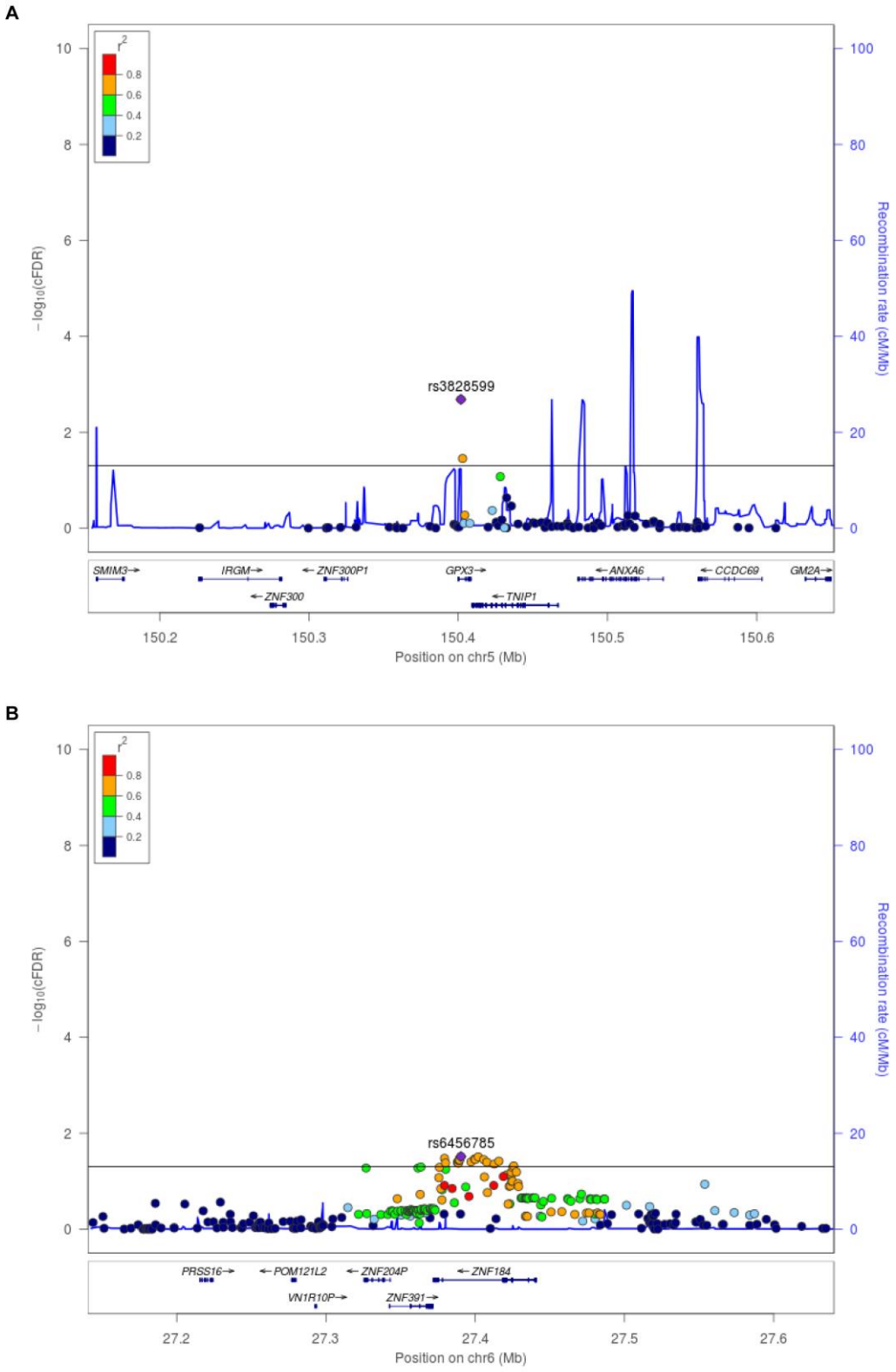
J


ALS | UC
-log10(cFDR)
Chromosomal location
C9orf72
MOB3B
GPX3
TNIP1
ERGIC1
LOC101927815
GLI3
BCAR3
GCFC2
NR1I3
ACSL5
ANO5
SDR9C7
KIF5A
LINC02403
C12orf56
TBK1
G2E3
SCFD1
TRIP11
ATXN3
KRT18P55
UNC13A
CFAP410

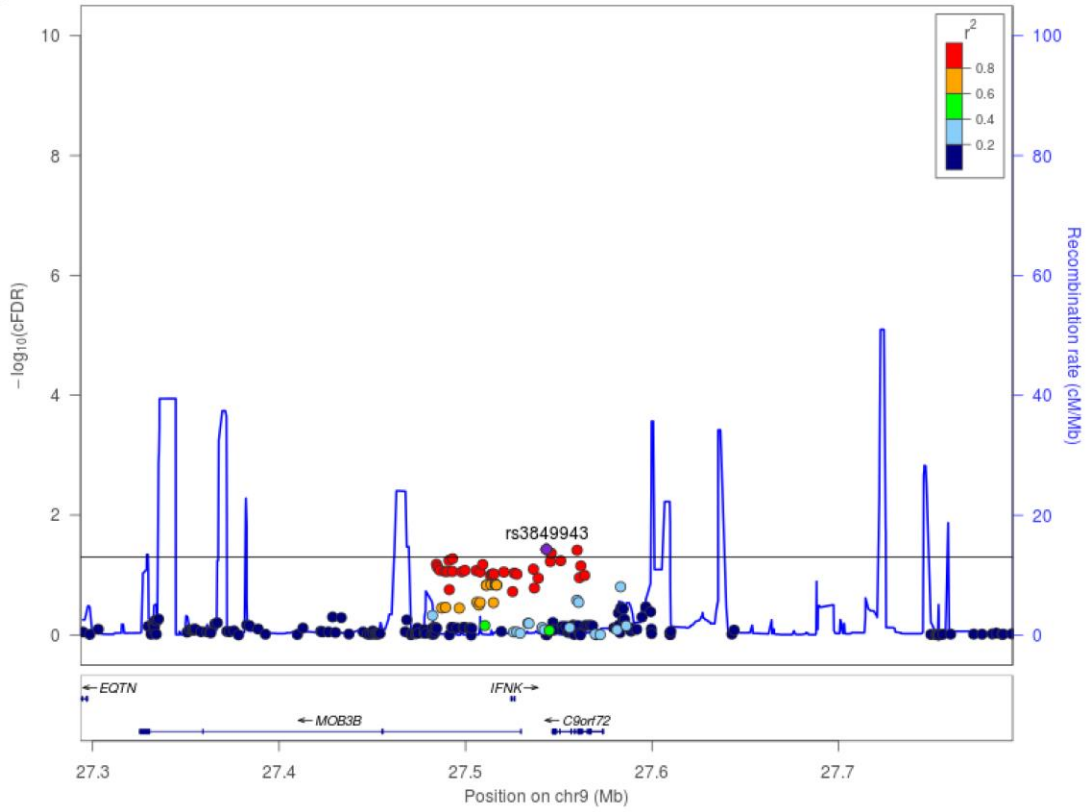


The horizontal line represents the significant threshold (conditional FDR < 0.01). The figure is suggested to view online for higher resolution.

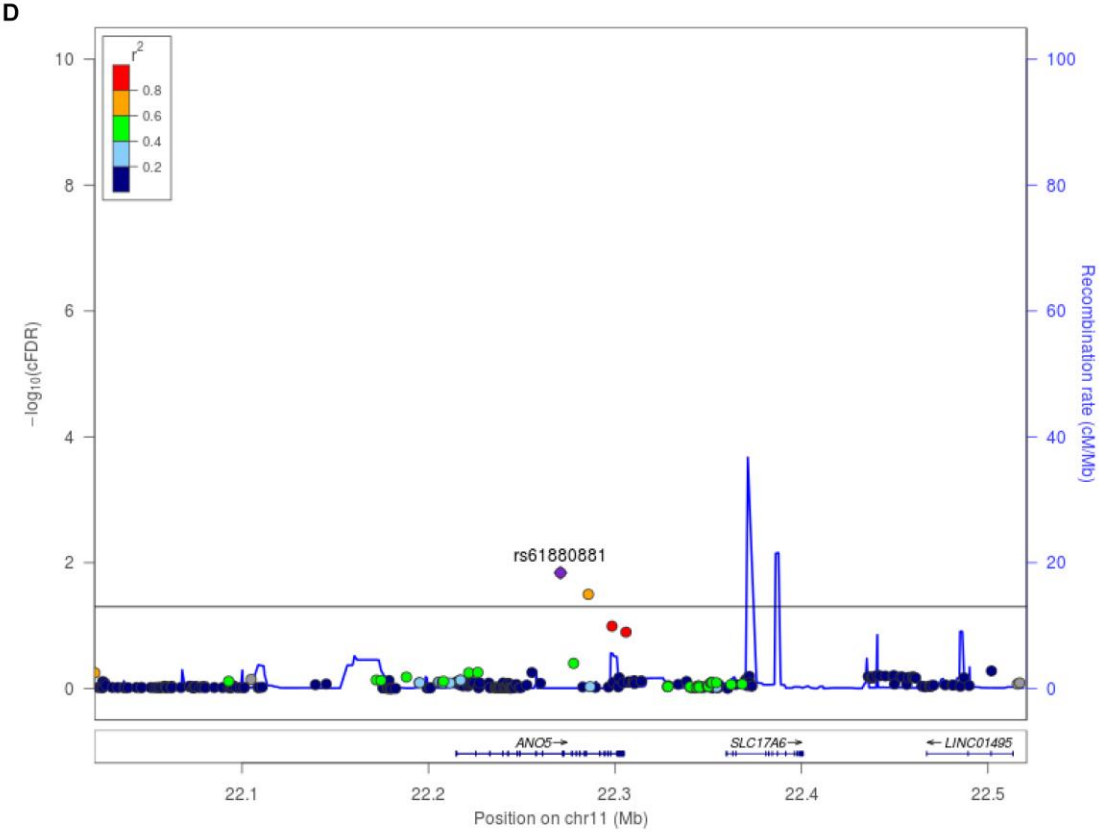
Figure S3. Regional association plots for shared risk loci between ALS and each autoimmune disease



C


r2
0.8
0.6
0.4
0.2
rs3849943
−log10(cFDR)
Recombination rate (cM/Mb)
EQTN
IFNK
MOB3B
C9orf72
Position on chr9 (Mb)

D


r2
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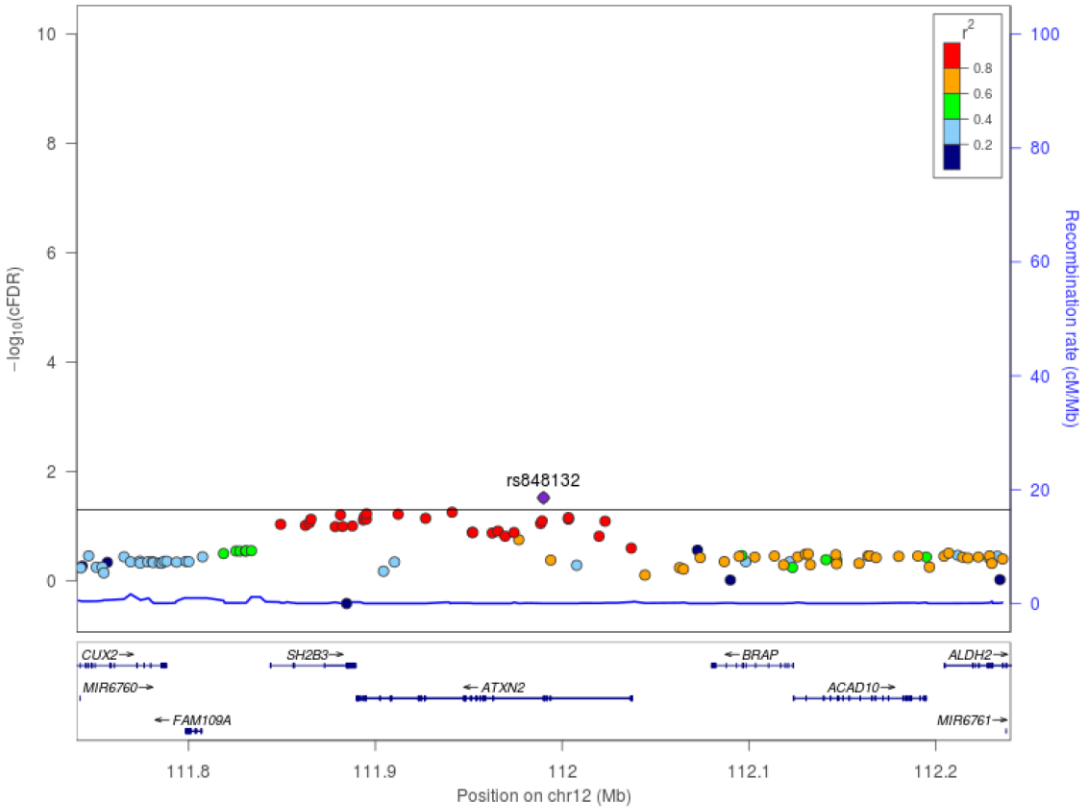
0.6
0.4
0.2
rs61880881
−log10(cFDR)
Recombination rate (cM/Mb)
ANO5
SLC17A6
LINC01495
Position on chr11 (Mb)

E


r2
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0.6
0.4
0.2
rs848132
−log10(cFDR)
Recombination rate (cM/Mb)
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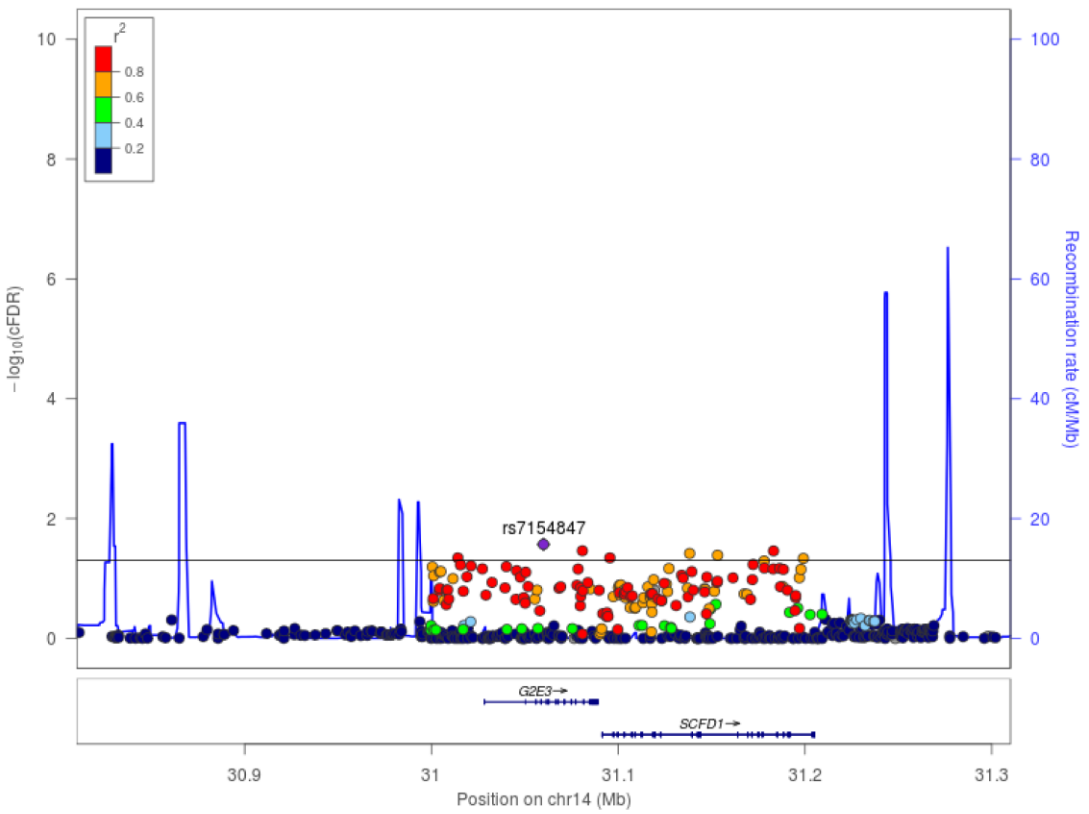
SH2B3
BRAP
ALDH2
MIR6760
ATXN2
ACAD10
FAM109A
MIR6761
Position on chr12 (Mb)

F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0.4
0.2
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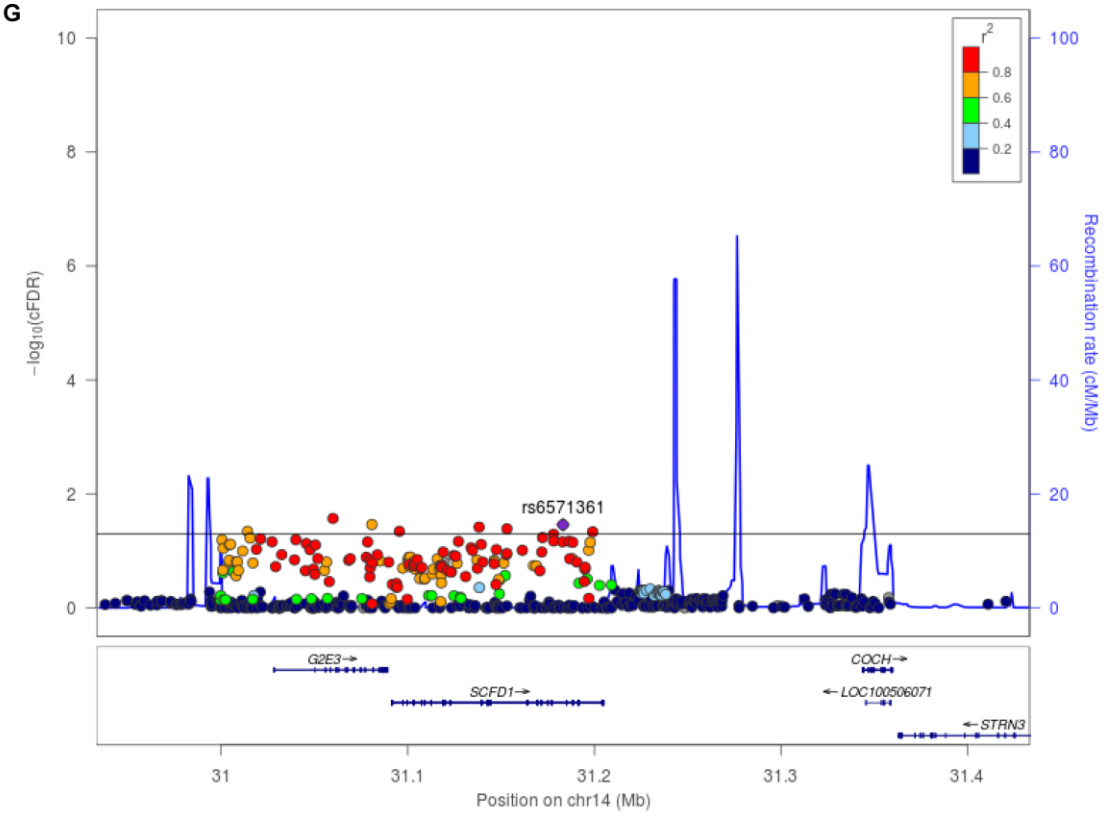
Recombination rate (cM/Mb)
G2E3
SCFD1
Position on chr14 (Mb)

G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0.4
0.2
rs6571361
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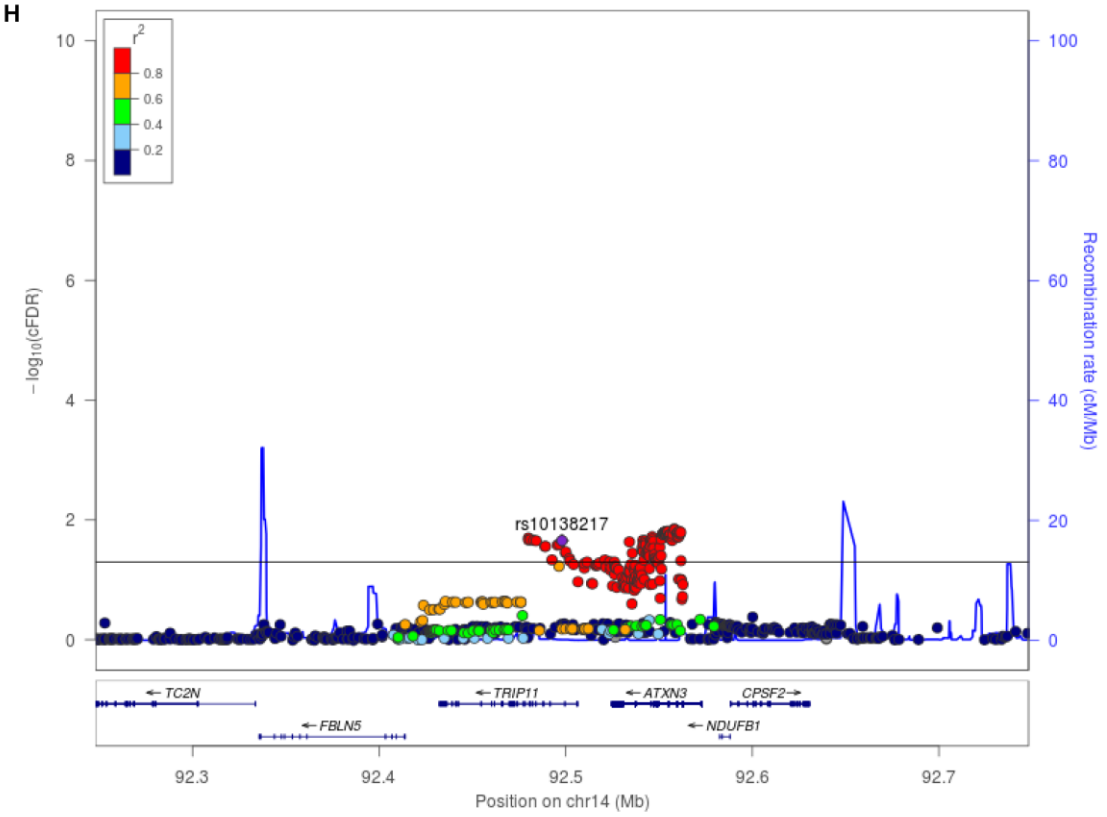
Recombination rate (cM/Mb)
G2E3
SCFD1
COCH
LOC100506071
STRN3
Position on chr14 (Mb)

H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0.4
0.2
rs10138217
−log10(cFDR)
Recombination rate (cM/Mb)
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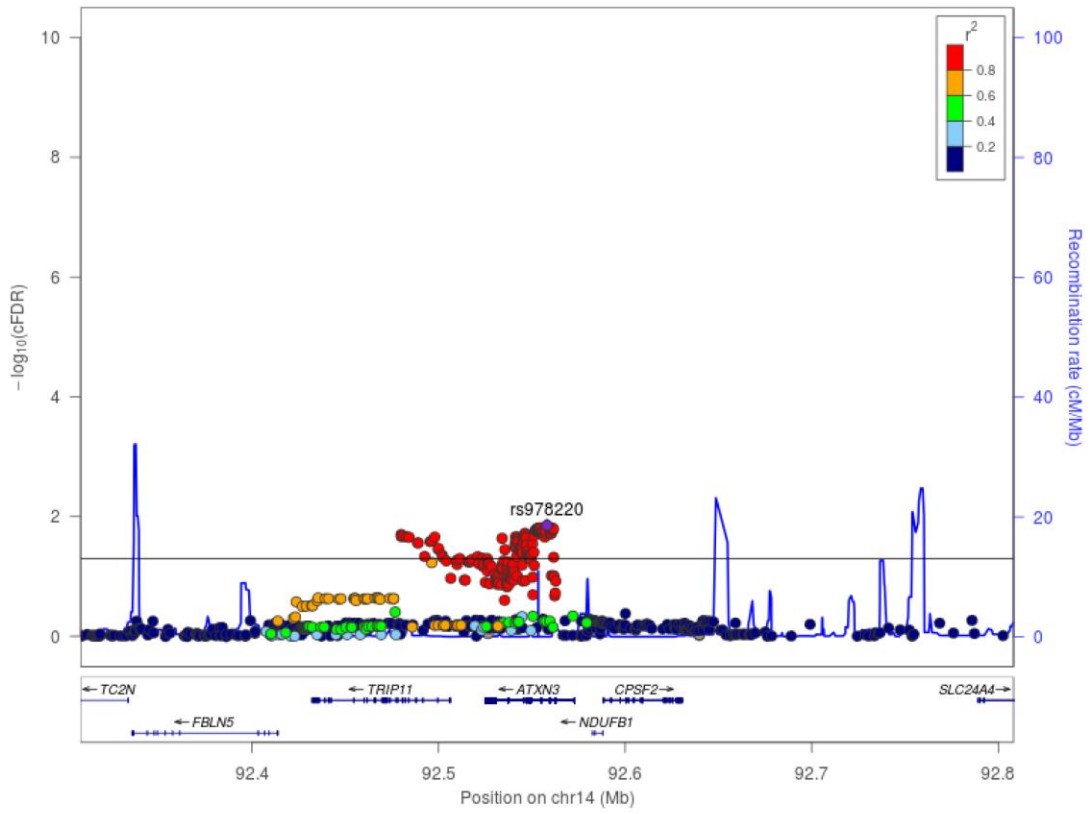
FBLN5
TRIP11
ATXN3
CPSF2
NDUFB1
Position on chr14 (Mb)

I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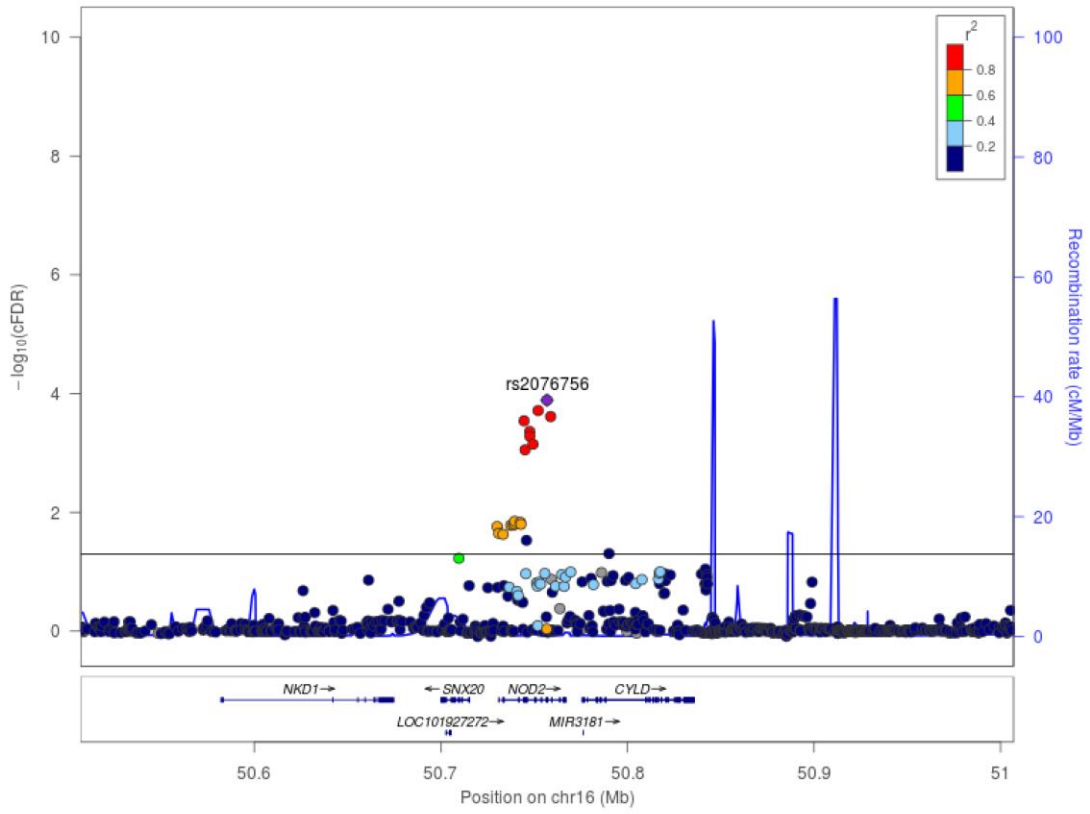
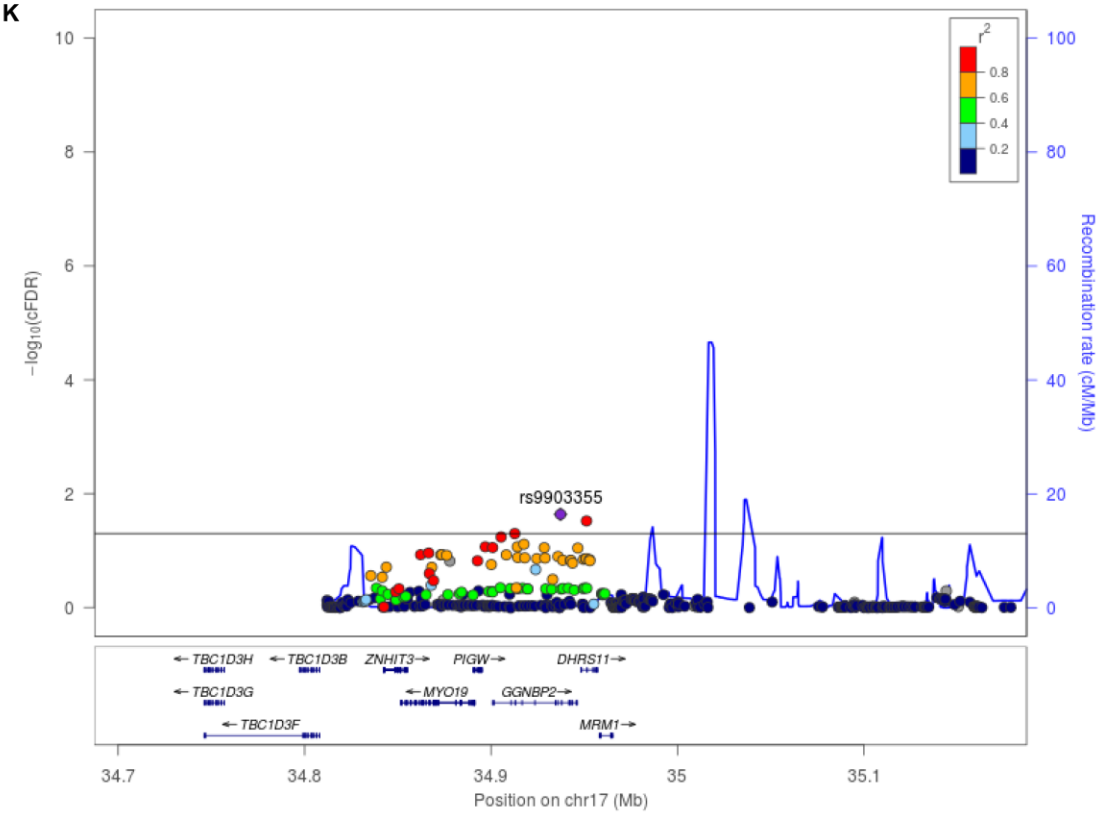
r2
0.8
0.6
0.4
0.2
−log10(cFDR)
Recombination rate (cM/Mb)
TC2N
TRIP11
ATXN3
CPSF2
SLC24A4
FBLN5
NDUFB1
92.4
92.5
92.6
92.7
92.8
Position on chr14 (Mb)

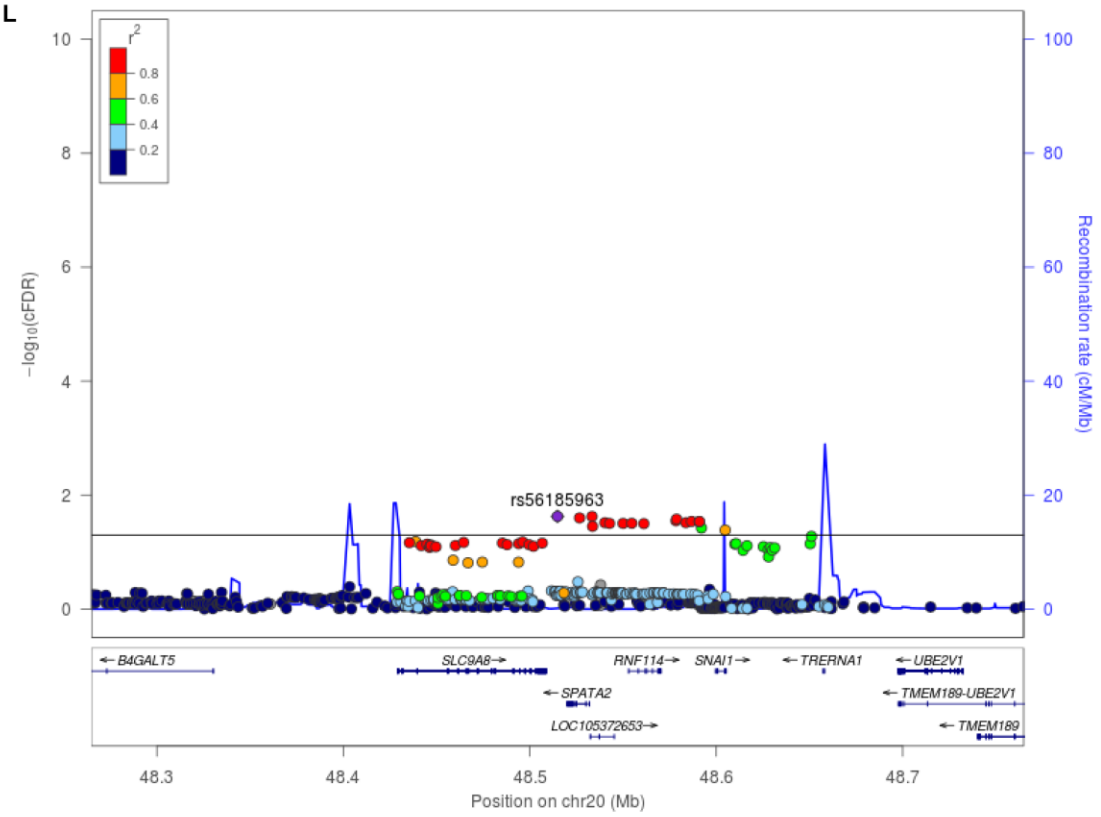
J

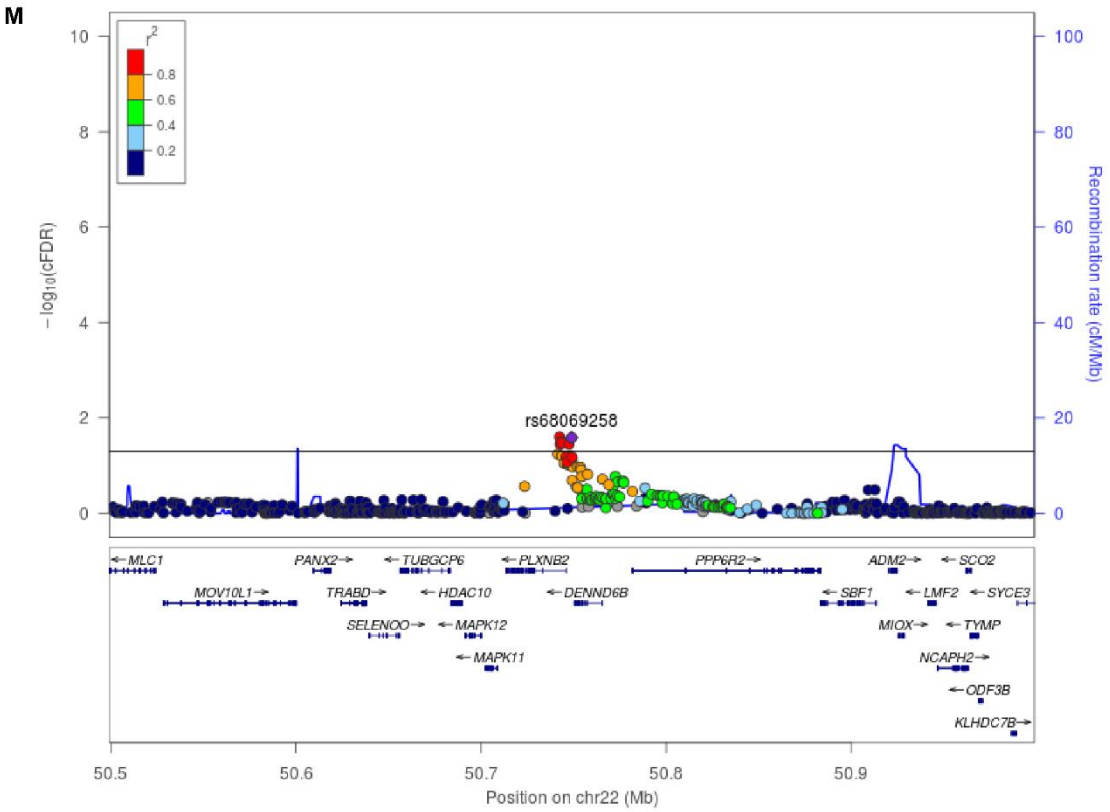

rs2076756
r2
0.8
0.6
0.4
0.2
−log10(cFDR)
Recombination rate (cM/Mb)
NKD1
SNX20
NOD2
CYLD
LOC101927272
MIR3181
50.6
50.7
50.8
50.9
51
Position on chr16 (Mb)

K


r2
0.8
0.6
0.4
0.2
rs9903355
−log10(cFDR)
Recombination rate (cM/Mb)
TBC1D3H
TBC1D3B
ZNHIT3
PIGW
DHRS11
TBC1D3G
MYO19
GGNBP2
TBC1D3F
MRM1
Position on chr17 (Mb)

L


r2
0.8
0.6
0.4
0.2
rs56185963
−log10(cFDR)
Recombination rate (cM/Mb)
B4GALT5
SLC9A8
RNF114
SNAI1
TRERNA1
UBE2V1
SPATA2
TMEM189-UBE2V1
LOC105372653
TMEM189
Position on chr20 (Mb)



The plots were generated using LocusZoom with default parameters. The horizontal line represents the significant threshold (conditional FDR < 0.05). The linkage disequilibrium was calculated using reference data derived from the 1000 Genomes Project European population. A flanking region of 250kb around target SNP was plotted.