SUPPLEMENTARY APPENDIX

Identification of a novel genetic locus associated with immune-mediated thrombotic thrombocytopenic purpura

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SUPPLEMENTARY MATERIALS

SUPPLEMENTARY METHODOLOGY

COHORTS

TTP cases were collected as described in the main paper between 2012 and 2017, with UK TTP cases (discovery cohort) and French TTP cases (replication cohort).

- UK TTP cases, n=413
- French TTP cases, n=200

The control cohorts include the 1958 British Birth Cohort and National Blood Service control samples, in addition to reference genotypes from the Illumina reference panel (HapMap Ethnicity controls) and Oxford controls.[1–5]

- Illumina Ethnicity Cohort, n=90
- Oxford Cohort, n=432
- British Birth Cohort, n=2867
- National Blood Service Cohort, n=2737

GENOTYPING

Samples were genotyped on the following SNP chips;

- UK TTP cases - HumanOmniExpress-12v1_H and 24v102_A1
- French TTP cases – HumanOmniExpress- 24v102_A1

Controls were genotyped on the following SNP chips;

- Illumina Reference - Illumina HumanOmniExpress-12v1_C
- Oxford controls - Illumina HumanOmniExpress-12v1_J
- British Birth Cohort - Human1-2M0DuoCustom_v1_A.
- National Blood Service Cohort - Human1-2M0DuoCustom_v1_A

Genotypes were re-encoded using in-house software to genomic forward for further analysis.[6]

QUALITY CONTROL

Quality control was performed using SNP & Variation Suite[7] PLINK version 1.90[8] and PRIMUS.[9]

Strict quality control per sample was performed, excluding individuals with call rate (CR) <0.90, duplicated samples/related individuals (sample identity by state (IBS) >0.1875), sample heterozygosity rate >3SD, in addition to excluding individuals not of European ancestry by principal component analysis (PCA) filtering.

Case Sample Quality control is summarised below;

- **UK TTP Cohort -** 241 UK TTP patients were included for subsequent analysis, from 413 samples genotyped.
- **French TTP Cohort** - 112 French TTP patients were included for subsequent analysis, from 200 samples genotyped.

Control Sample Quality control is summarised below;

- **Illumina Ethnicity Controls** - 58 individuals were included for subsequent analysis, from 90 samples genotyped.
- **Oxford Controls** - 381 individuals were included for subsequent analysis, from 432 samples genotyped.
- **British Birth Cohort** - 2761 individuals were included for subsequent analysis, from 2867 samples genotyped.
- **National Blood Service Cohort** - 2603 individuals were included for subsequent analysis, from 2737 samples genotyped.

Quality control was performed per SNP, and SNPs were excluded with that had a CR<0.99, an allele count (AC) >2, minor allele frequency (MAF) <0.05, and Hardy Weinberg Equilibrium (HWE) p<0.001, non-autosomal markers, in addition to ambiguous SNPs.

Case SNP Quality Control is summarised below;

- **UK TTP Cohort** - QC was performed on 675,533 SNPs, and post QC 521,046 SNPs remained.

- **French TTP Cohort** - QC was performed on 675,533 SNPs, and post QC 490,032 SNPs remained.

Control SNP Quality Control is summarised below;

- **Illumina Ethnicity Controls** - QC was performed on 711,320 SNPs, and post QC 531,093 SNPs remained.
- **Oxford Controls** - QC was performed on 712,878 SNPs, and post QC 567,947 SNPs remained.
- **British Birth Cohort** - QC was performed on 1,066,003 SNPs, and post QC 722,672 SNPs remained.
- **National Blood Service Cohort** - QC was performed on 1,066,003 SNPs, and post QC 736,251 SNPs remained.

The UK and French datasets were combined with separate control datasets, and the above per-SNP QC performed on the merged datasets

- **UK Discover Cohort** - The UK TTP cohort (n=241) was combined with control datasets (Illumina Ethnicity, Oxford and British Birth cohorts) (n=3200) for overlapping SNPs (n=337,088).
- **French Replication Cohort** - The French TTP cohort (n=112) was combined with control datasets (National Blood Service cohort) (n=2603) for overlapping SNPs (n=334,756).

IMPUTATION

Genotype data was imputed using Beagle version 5.0, utilising the 1000 Genome European CEU reference population (Supplemental Figure 1 for QC).[10] Cases and controls were imputed together using individuals and markers that had previously passed stringent QC. Following imputation filtering was performed using bcftools[11] (https://samtools.github.io/bcftools/bcftools.html), and markers with a Dosage R-squared (DR2) less than 0.80 were removed, and imputed genotype data was also re-filtered per SNP using SNP & Variation Suite,[7] details listed below:

- The UK TTP cohort and control data sets were imputed, with indels and SNPs with DR2<0.80 excluded. Post QC 3,649,349 remained for analysis, and

further QC SNP's were excluded, CR<0.99, AC>2 (n=0), MAF<0.05, HWE p<0.001.

- The French TTP cohort and control data was imputed, and indels and SNPs with DR2<0.80 were excluded. Post QC n=3,649,546 remained for analysis, and further QC SNP's were excluded, CR<0.99, AC>2, MAF<0.05 and HWE p<0.001.

GENOME WIDE ASSOCIATION TESTING

Genome wide association testing was performed using SNP & Variation Suite, using logistic regression with correction of 10 principal components.[12–14] The logistic regression p-values, odds ratios were calculated in addition to Lambda inflation factors. A standardised genome wide significance level of $5x10^{-8}$ was applied.[15] Meta-analysis was performed by combining the independent cohorts and subsequently undertaking analysis by logistic regression with 10 principal component correction.

CONDITIONAL ANALYSIS

To investigate for independent signal conditional analysis was undertaken using a full versus reduced regression model in SVS. Lead SNPs were used as conditional inputs to determine independence, with results plotted using Locus Zoom software.[16]

HLA IMPUTATION

HLA imputation was performed utilising SNP2HLA to impute HLA types using previously genotyped markers.[17] Imputed HLA types were excluded if the DR2 (confidence) was <0.80. Conditional analysis was subsequently performed, using the previously described method. To validate our HLA imputation, we compared imputed HLA types in a subset of serologically HLA typed individuals (n=17), and found a concordance of >80%.

EXPRESSION QUANTITATIVE TRAIT LOCUS

Expression quantitative trait locus analysis was performed subsequently to associate identified SNPs with differential gene expression.[18] Reduced POGLUT1 expression associated with our haploblock was the most significant, and frequently reported

association, and the only gene with expression reduced across different platforms.[18,19]

LD-LINK

Additional markers in linkage disequilibrium with our lead SNP were identified by LD-link (https://ldlink.nci.nih.gov).[20] LD between variants rs71767581 and rs9884090 was supported using the NIHR BioResource-Rare Diseases dataset, comprising whole genome sequences from 6,588 European individuals.[21]

FUNCTIONAL ANNOTATION

Functional annotation of the haploblock was performed using the UCSC genome browser (https://genome.ucsc.edu)[22,23], to identify functional important variants. Functional annotations, Chip-Seq data and expression data to identify functionally important variants such as missense variants or regulatory variants.

FACTOR BOOK

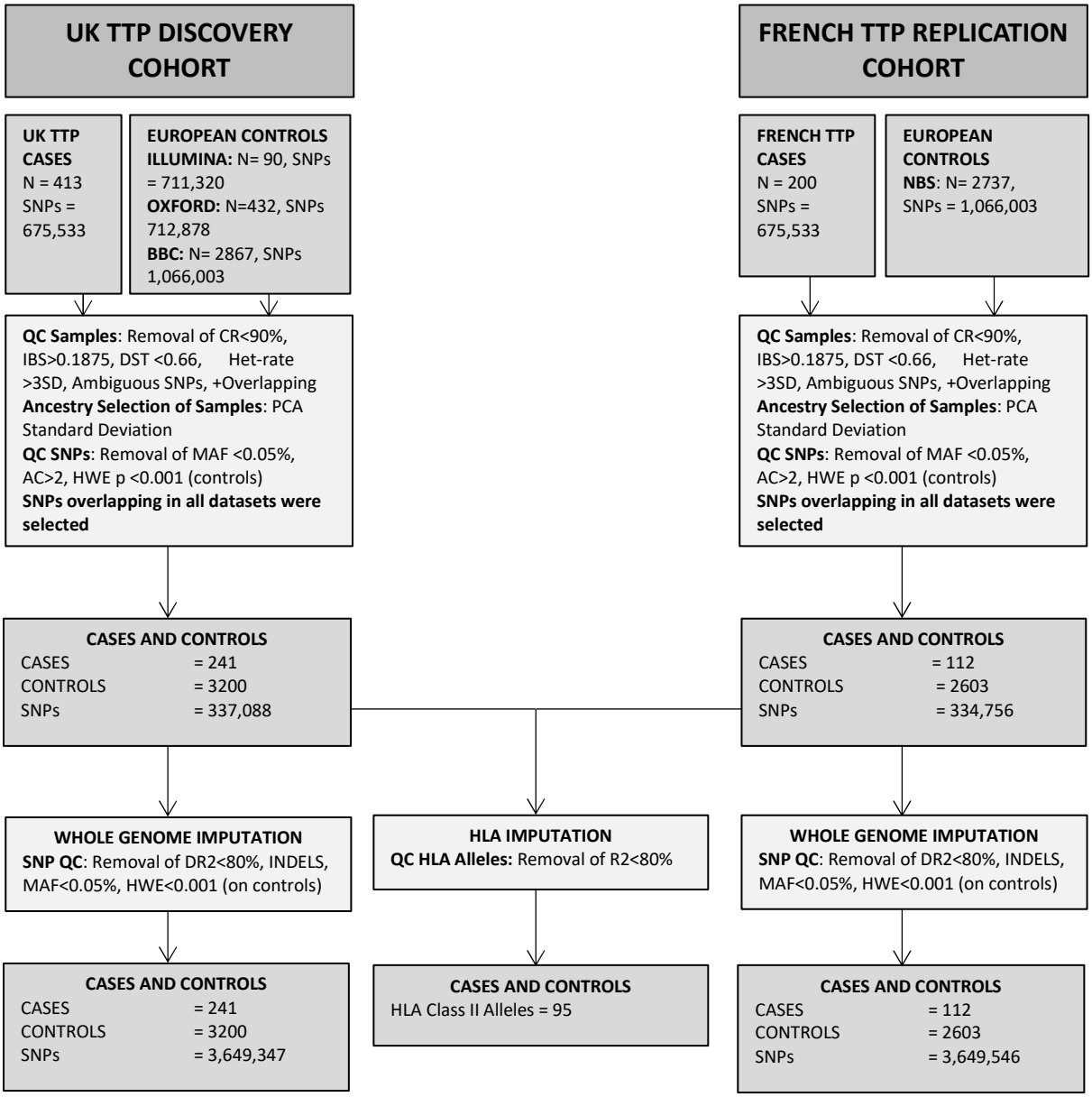
Binding sites of transcription factors that were identified through functional annotation in the region of interest, with potential functional importance were obtained from FactorBook.[24] Searching for specific cells lines (HEPG2) the position weight matrix (PWM) binding motifs of transcription factors of interest were identified, to be analysed alongside genetic variants derived from UCSC genome browser.

MAST/MEME

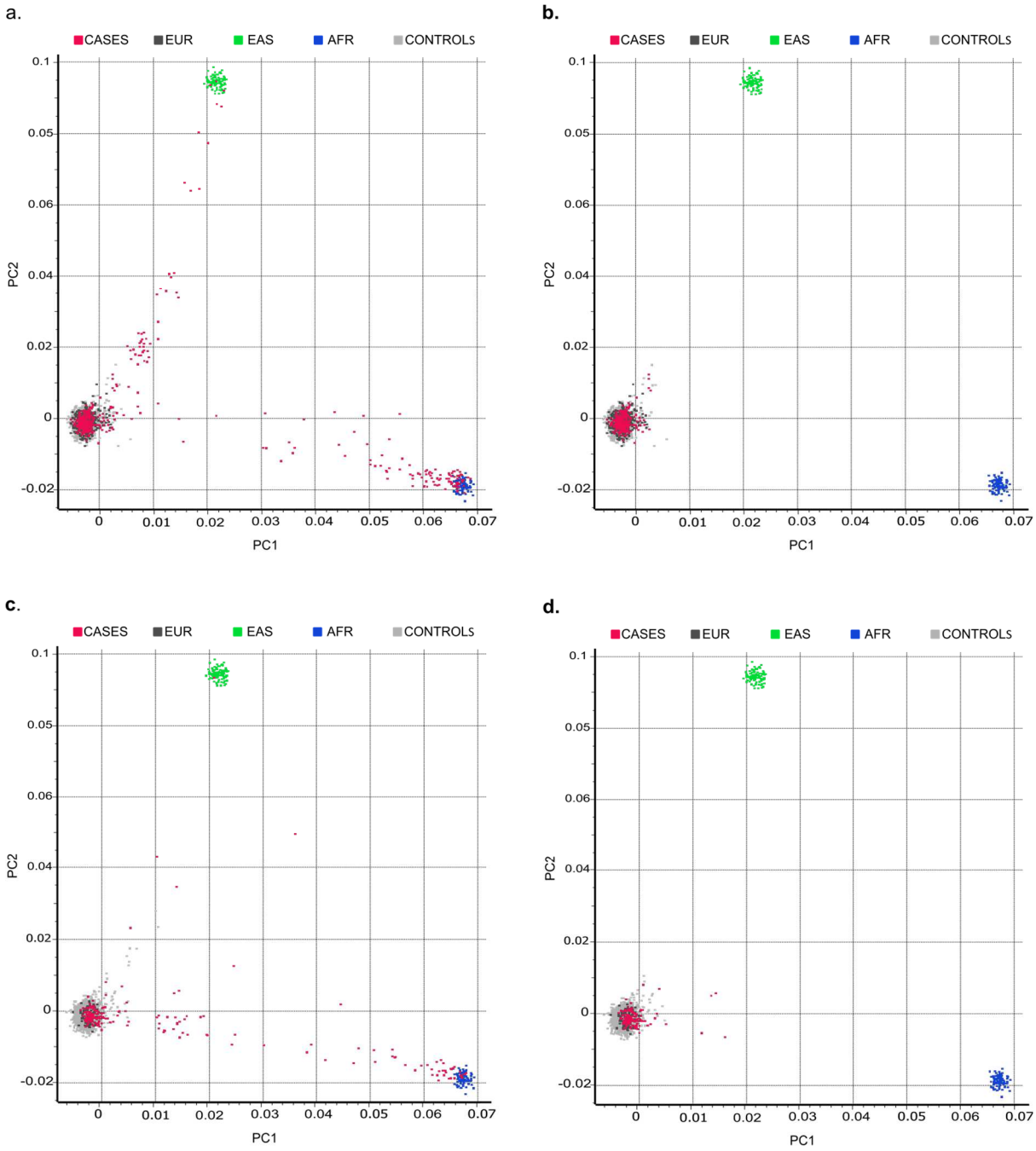
PWM binding motifs that were obtained from factor book were analysed along-side haploblock genetic variants, obtained from UCSC. A 80bp DNA sequence (40bp flanking, listed below) were analysed for potential DNA-transcription factor binding).[25]

- Wide Type Sequence: TATGCTAATTGCAACCTTTGGGGTCTAACCGTGC TGTACACACACACACACACACACACACACACACACACACACATGCTCA
- Variant Sequence: TATGCTAATTGCAACCTTTGGGGTCTAACCGTGCTGT -/- ACACACACACACACACACACACACACACACACACACACATGCTCA

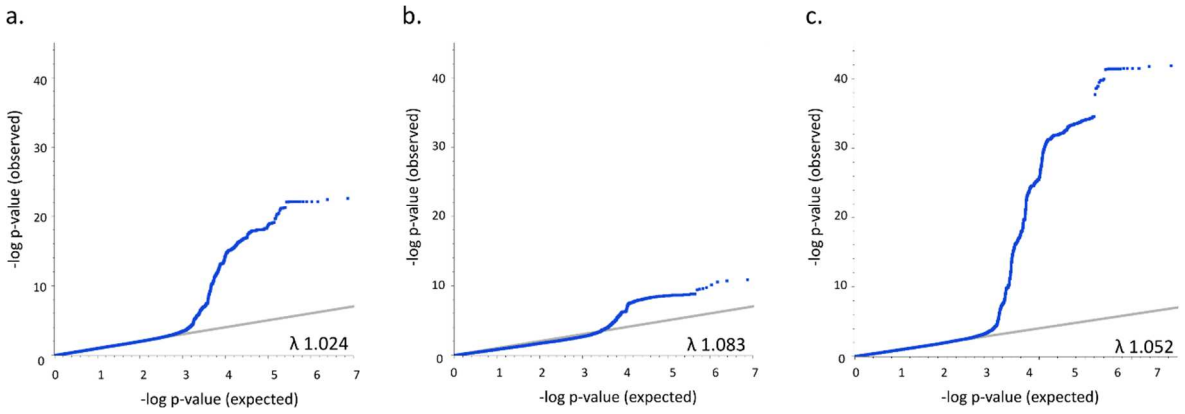
SUPPLEMENTARY FIGURES / RESULTS



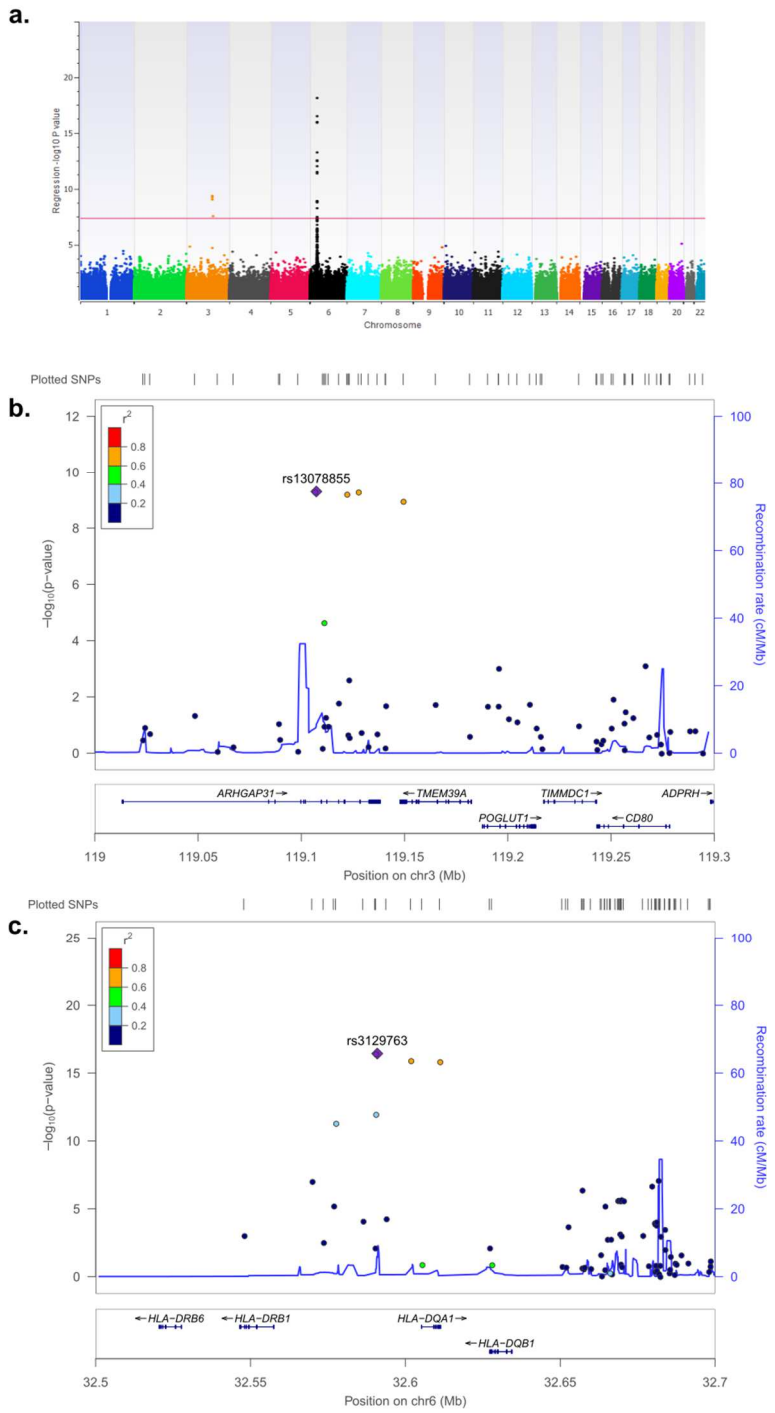
Supplemental Figure 1 – Summary of Quality Control in UK Discovery Cohort and French Replication Cohort.



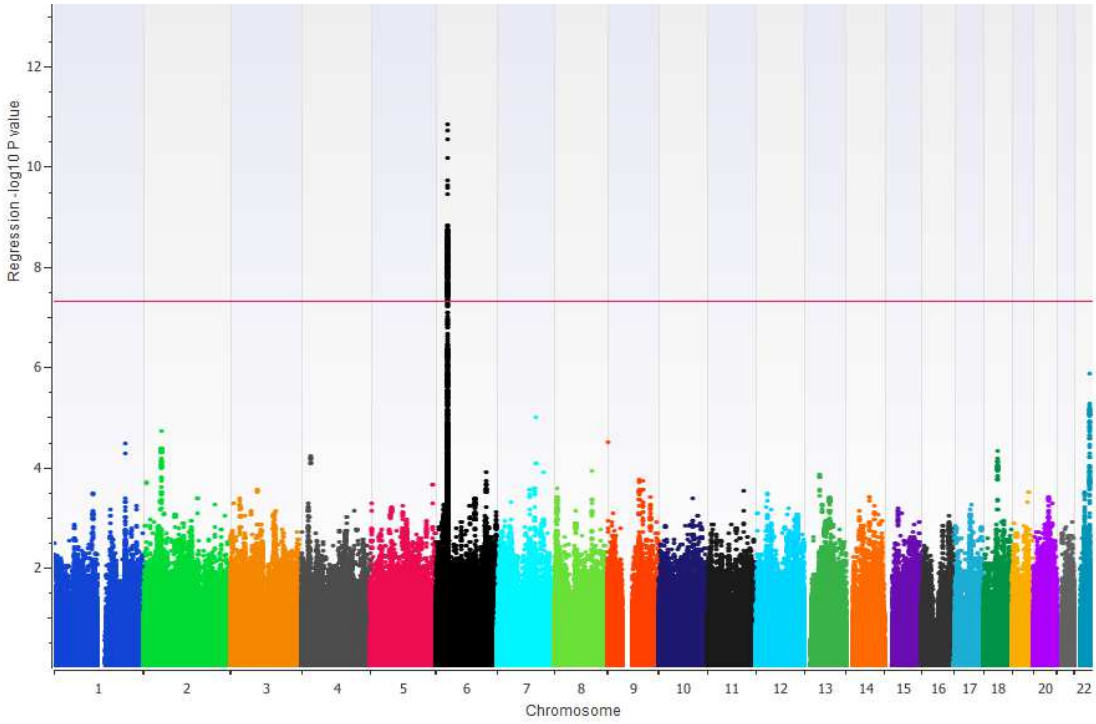
Supplemental Figure 2 – Principal Component Analysis in UK and French Cohorts. Cases are shown in red, and control genotypes in grey, and controls with known genetic ancestry are shown in black (EUR, European), blue (AFR, African) and green (EAS, East Asian). a. UK discovery cohort (without ethnicity ancestry filtering) and b. UK discovery cohort following ethnicity ancestry filtering applying 8.0 standard deviations to the principal component data to select cases with European ancestry. c. French replication cohort (without ethnicity ancestry filtering) and d. French replication cohort following ethnicity ancestry filtering applying 8.0 standard deviations to the principal component data to select cases with European ancestry.



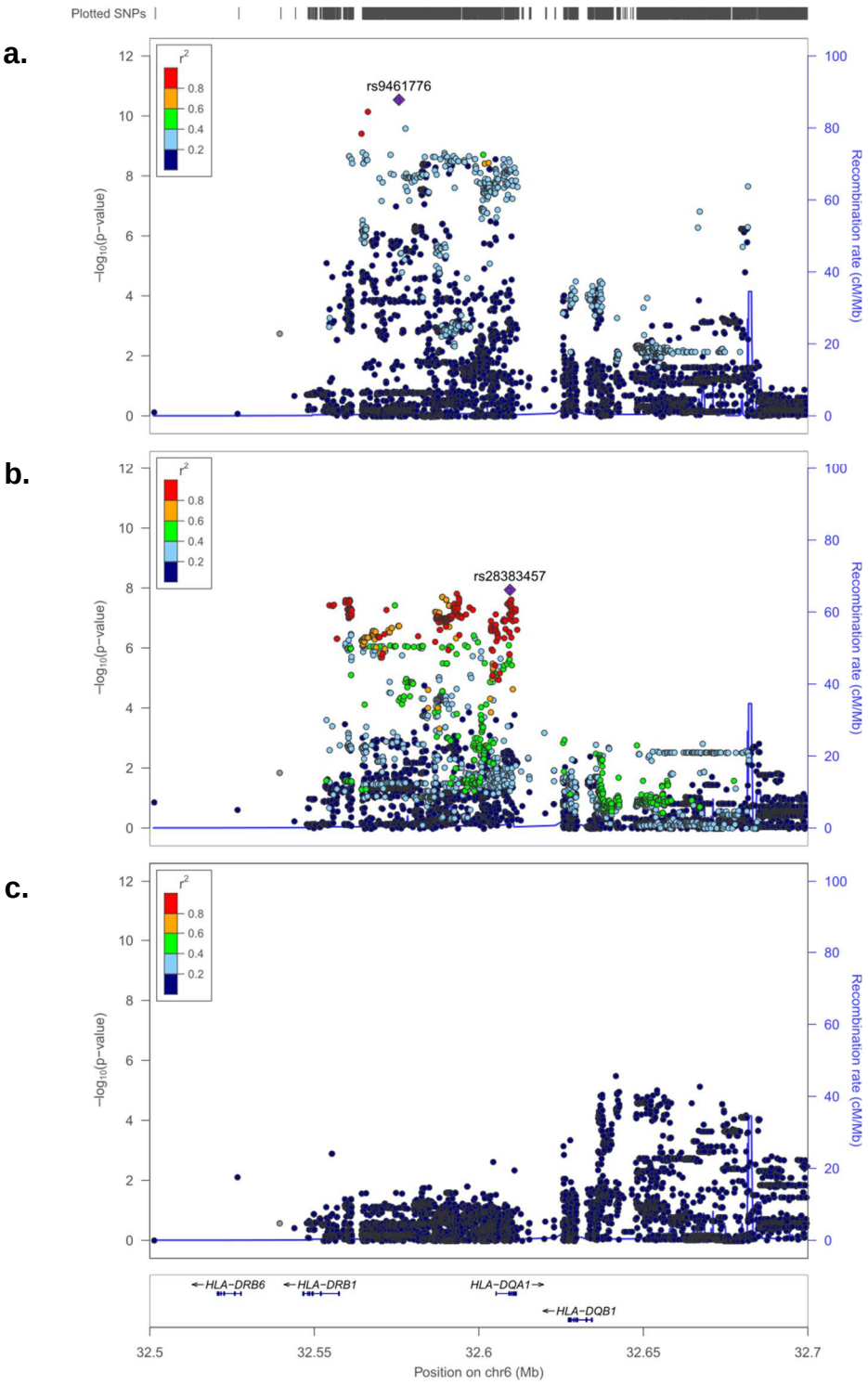
Supplemental Figure 3 – QQ plots, observed against expected p-values, for a. UK discovery population, b. French replication cohort, and c. Combined Analysis.



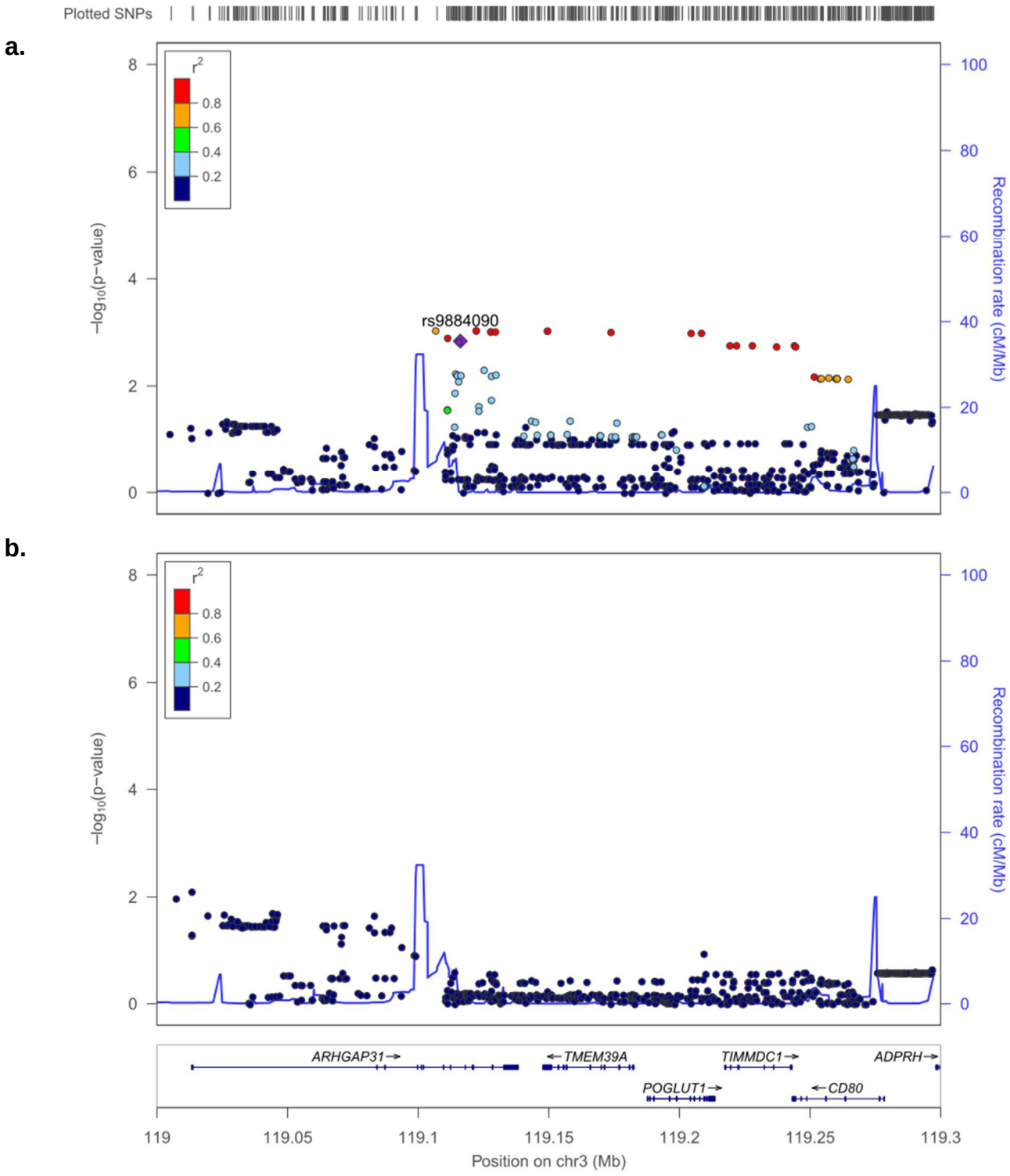
Supplemental Figure 4 – UK Cohort Directly Genotyped GWAS - (a) Manhattan plot of genome wide association test for directly genotyped SNPs only, comparing UK cases against controls, utilising the logistic regression method, corrected for top 10 principal components for stratification. The X axis shows chromosome location, and the Y axis shows logarithmic p-values. Standardised genome wide significant $5x10^{-8}$ is depicted by the red line. Locus zoom plot for the UK discovery cohort (visualising only directly genotyped SNPs) are shown for (b) chromosome 3 and (c) and chromosome 6 peak. The X axis shows chromosome location, and the left Y axis shows logarithmic p-values (logistic regression), and the right Y axis shown the recombination rate (shown as the blue line) (Human Assembly GRCh37/hg19).



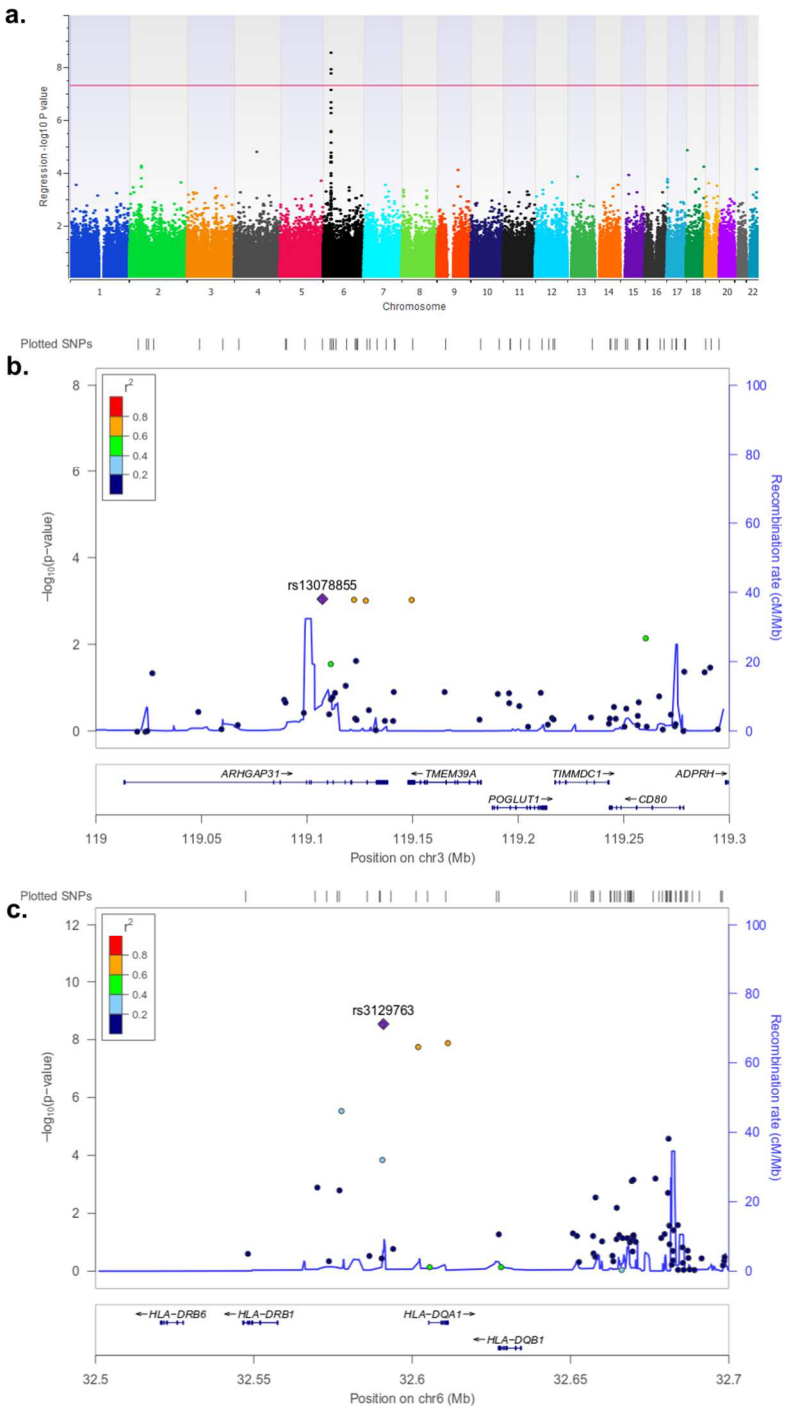
Supplemental Figure 5 – French Cohort Imputed GWAS – Manhattan plot of genome wide association test comparing French Replication cohort compared against controls, utilising the logistic regression method, corrected for top 10 principal components for stratification, in all imputed SNPs. The X axis shows chromosome location, and the Y axis shows logarithmic p-values. Standardised genome wide significant $5x10^{-8}$ is depicted by the red line. The HLA peak is visualised on chromosome 6 (black).



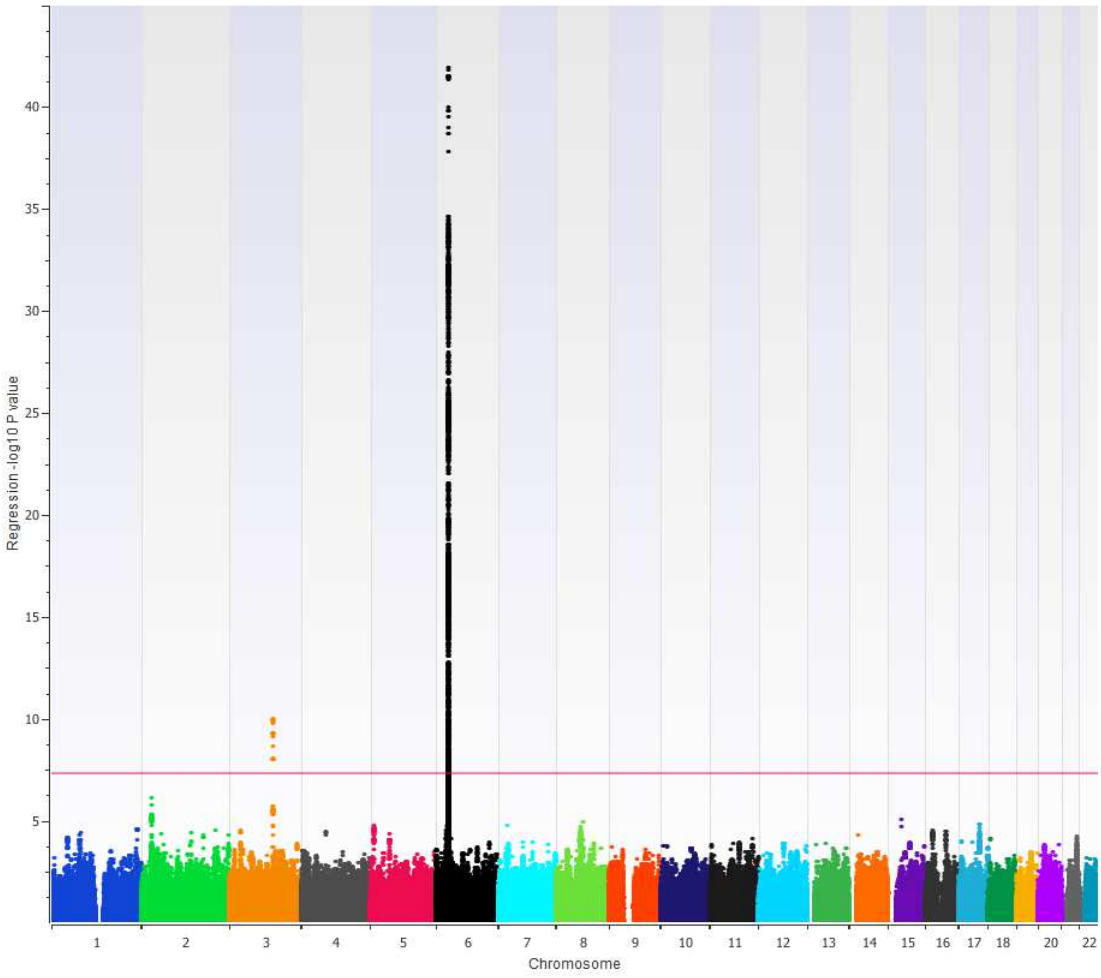
Supplemental Figure 6 – Locus zoom plot of the chromosome 6 peak in the French replication cohort. Genomic area displayed is 32.5 Mb to 32.7 Mb on chromosome 3 (Human Assembly GRCh37/hg19). The X axis shows chromosome location, and the left Y axis shows logarithmic p-values (logistic regression), and the right Y axis shown the recombination rate (shown as the blue line). a. shows the unconditional analysis with the lead SNP rs9461776, b. shows conditional analysis conditioned on rs9461776, revealing an independent association signal, lead SNP rs28383457, and c. shows analysis conditioned on conditioned on rs9461776 and rs28383457.



Supplemental Figure 7 – Locus zoom plot of the chromosome 3 peak in the French Replication cohort. Genomic area displayed is 119.0 Mb to 119.3 Mb on chromosome 3 (Human Assembly GRCh37/hg19). The X axis shows chromosome location, and the left Y axis shows logarithmic p-values (logistic regression), and the right Y axis shown the recombination rate (shown as the blue line). a. shows the unconditional analysis with the lead SNP rs9884090. b shows the same region containing the same markers, following conditioning on rs9884090 (identified from the UK discovery cohort analysis).



Supplemental Figure 8 – French Cohort Directly Genotyped GWAS - (a) Manhattan plot of genome wide association test for directly genotyped SNPs only, comparing French cases against controls, utilising the logistic regression method, corrected for top 10 principal components for stratification. The X axis shows chromosome location, and the Y axis shows logarithmic p-values. Standardised genome wide significant $5x10^{-8}$ is depicted by the red line. Locus zoom plot for the French replication cohort (visualising only directly genotyped SNPs) are shown for (b) chromosome 3 and (c) and chromosome 6 peak. The X axis shows chromosome location, and the left Y axis shows logarithmic p-values (logistic regression), and the right Y axis shown the recombination rate (shown as the blue line) (Human Assembly GRCh37/hg19).



Supplemental Figure 9 – GWAS Meta-Analysis of UK and French Cohorts - Manhattan Plot of Genome wide association tests for the meta-analysis of UK and French combined cohorts, utilising the logistic regression method, corrected for top 10 principal components for stratification. The X axis shows chromosome location, and the Y axis shows logarithmic p-values. Standardised Genome wide significant $5x10^{-8}$ is displayed in as the red line. The HLA peak is visualised on chromosome 6 (black, grey), in addition to the novel chromosome 3 association (orange, grey).

RS_ID	Location (GRCh37/hg19)	Alleles	MAF	Distance	D'	R2	Functional Annotation
rs9884090	chr3:119116150	(G/A)	0.1364	0	1	1	ARHGAP31 INTRON
rs9834901	chr3:119111870	(T/C)	0.1364	-4280	1	1	ARHGAP31 INTRON
rs12494314	chr3:119122820	(T/C)	0.1364	6670	1	1	ARHGAP31 INTRON
rs2305249	chr3:119128398	(G/A)	0.1364	12248	1	1	ARHGAP31 EXON (SYNON)
rs9855065	chr3:119130141	(G/A)	0.1364	13991	1	1	ARHGAP31 INTRON
rs3732421	chr3:119150089	(A/G)	0.1364	33939	1	1	TMEM39A 3'UTR
rs7650774	chr3:119205050	(T/C)	0.1364	88900	1	1	POGLUT1 INTRON
rs12695386	chr3:119209027	(T/C)	0.1364	92877	1	1	POGLUT1 CTCF
rs12636784	chr3:119174383	(A/G)	0.1313	58233	1	0.95	TMEM39A INTRON
rs2293370	chr3:119219934	(G/A)	0.1515	103784	1	0.88	TIMMDC1 TFBS
rs1131265	chr3:119222456	(G/C)	0.1515	106306	1	0.88	TIMMDC1 EXON (SYNONYMOUS)
rs9843355	chr3:119228508	(G/A)	0.1515	112358	1	0.88	TIMMDC1 INTRON
rs144104218	chr3:119237726	(AAC/-)	0.1515	121576	1	0.88	TIMMDC1 INTRON
rs62264485	chr3:119237798	(C/A)	0.1515	121648	1	0.88	TIMMDC1 INTRON
rs35264490	chr3:119238753	(A/-)	0.1515	122603	1	0.88	TIMMDC1 INTRON
rs57271503	chr3:119244593	(G/A)	0.1515	128443	1	0.88	CD80 EXON ENHANCER
rs13092998	chr3:119245044	(G/T)	0.1515	128894	1	0.88	CD80 INTRON
rs3830649	chr3:119246385	(G/-)	0.1515	130235	1	0.88	CD80 INTRON
rs71767581	***chr3:119187433***	***(AC/-)***	***0.1364***	***71283***	***0.91***	***0.84***	***POGLUT1 TFBS***
rs1132200	chr3:119150836	(C/T)	0.1162	34686	1	0.83	TMEM39A EXON (MISSENSE)

Supplemental Table 1 – Additional SNP's identified from LD-Link, found to be in Linkage disequilibrium with rs9884090 (lead chromosome 3 haploblock 3, identified through GWAS). SNP's with R^2 and D' >0.80 are shown. Functional annotations (derived from UCSC) are also included.

Transcription Factors
TCF12
GATA1
JUND
CHD1
MYBL2
TEAD4
STAT5A
POLR2A
NR3C1
RELA
REST
YY1
E2F6
PHF8

Supplemental Table 2 – Transcription factors, identified from UCSC that have ChipSeq tracts overlaying the proposed functional variant rs71767581.

Supplemental Results

Several other SNPs within the haploblock containing rs9884090 have also been implicated with other autoimmune disease. Previously published SNPs were analysed for linkage with rs9884090 (D' and R^2) using LD-link (with 1000G European CEU reference panel)[20] and also searched for any evidence of eQTL using GTEX, particularly indicating any evidence of altered POGLUT1 expression. The LD (D' and R2 shown) and also eQTL data is shown below for different autoimmune disease. Notably the eQTL data was not included in the for the majority of the initial studies.

SNPs associated with Multiple Sclerosis

- rs1132200, D' 1.0 R^2 0.83, Reduced POGLUT1 expression on eQTL analysis.[26,27]

SNPs associated with Systemic Lupus Erythematosus

- rs1132200; D' 1.0 R^2 0.83, Reduced POGLUT1 expression on eQTL analysis.[28]
- rs12494314, D' 1.0, R^2 1.0, Reduced POGLUT1 expression on eQTL analysis (in addition to TIMMDC1).[29]
- rs12493175, D' 1.0, R^2 0.04, Reduced POGLUT1 on eQTL analysis.(30)
- rs13062955,D' 1.0, R^2 0.04, No eQTL data available.[30]

SNPs associated with Autoimmune Thyroid Disease

- rs12492609, D' 1.0, R^2 0.036, No eQTL data available.[31]
- rs7629750, D' 1.0, R^2 0.27, No eQTL data available.[31]

SNPs associated with Primary Biliary Cholangitis

- rs2293370, D' 1.0, R^2 0.88, Reduced POGLUT1 expression on eQTL analysis, which was reported in the published paper.[32]

The above results demonstrate that the majority of SNPs associated with different autoimmune disease within this haploblock have evidence of strong linkage with rs9884090, and where available eQTL demonstrates altered POGLUT1 expression.

SUPPLEMENTAL WEBLINKS

- WTCCC[1]
  WTCCC Available from the European Genome Archive,
  http://www.wtccc.org.uk

- Golden Helix, SNP and Variation Suite (SVS)[7]
  Details of SVS available from http://www.goldenhelix.com (Bozeman)

- PLINK[8]
  Software available from http://www.cog-genomics.org/plink/1.9

- PRIMUS[9]
  Primus available from http://primus.gs.washington.edu/primusweb/index.html

- Beagle[10]
  Software available from http://faculty.washington.edu/browning/beagle/

- Locus Zoom[16]
  Locus Zoom web platform access via http://locuszoom.org

- SNP2HLA[17]
  SNP2HLA software available from
  http://software.broadinstitute.org/mpg/snp2hla

- LD-LINK[20]
  LD-link online platform available from https://ldlink.nci.nih.gov

- UCSC genome browser[22,23]
  UCSC Genome browser available from https://genome.ucsc.edu

- FACTOR BOOK[24]
  Factor book online software available at www.factorbook.org

- MASTMEME[25]
  Mast-Meme online software available at https://meme-suite.org

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