Genetic evidence for serum amyloid P component as a drug target for treatment of neurodegenerative disorders

Supplementary information

Schmidt *et al*.

Contents

Figures

S1 Correlation between SomaLogic values and immunoassay for actual plasma SAP concentration . . . 2
S2 Locus view plots . . . 6
S3 GWAS Catalog look-ups . . . 9

Tables

S1 Lead variants for serum amyloid P component (SAP) plasma concentration . . . 11
S2 SAP lead variant associations with plasma C-reactive protein (CRP) concentration . . . 12
S3 Open target v2g results mapping *trans*-variant rs2808467 to a putative causal gene . 13
S4 Open target v2g results mapping *trans*-variant rs165316 to a putative causal gene . . 14
S5 Open target v2g results mapping *trans*-variant rs10188292 to a putative causal gene . 15
S6 Open target v2g results mapping *trans*-variant rs4665972 to a putative causal gene . 16
S7 Open target v2g results mapping *trans*-variant rs112875651 to a putative causal gene 17
S8 Open target v2g results mapping *trans*-variant rs9591359 to a putative causal gene . 18
S9 GWAS Catalog look-ups for putative causal genes for plasma SAP value. . . . 19
S10 The *cis*-Mendelian randomization results for the effects of one standard deviation higher plasma SAP value or plasma CRP concentration on dementia outcomes. . . . 20
S11 The *cis*-Mendelian randomization results for the effects of one standard deviation higher plasma SAP value on secondary outcomes . . . 21
S12 The *cis*-Mendelian randomization results for the effects of one standard deviation higher plasma CRP concentration on secondary outcomes . . . 23
S13 The *cis*-multivariable Mendelian randomization results for the effects of one standard deviation higher plasma SAP value or plasma CRP concentration. . . . 24

Figures

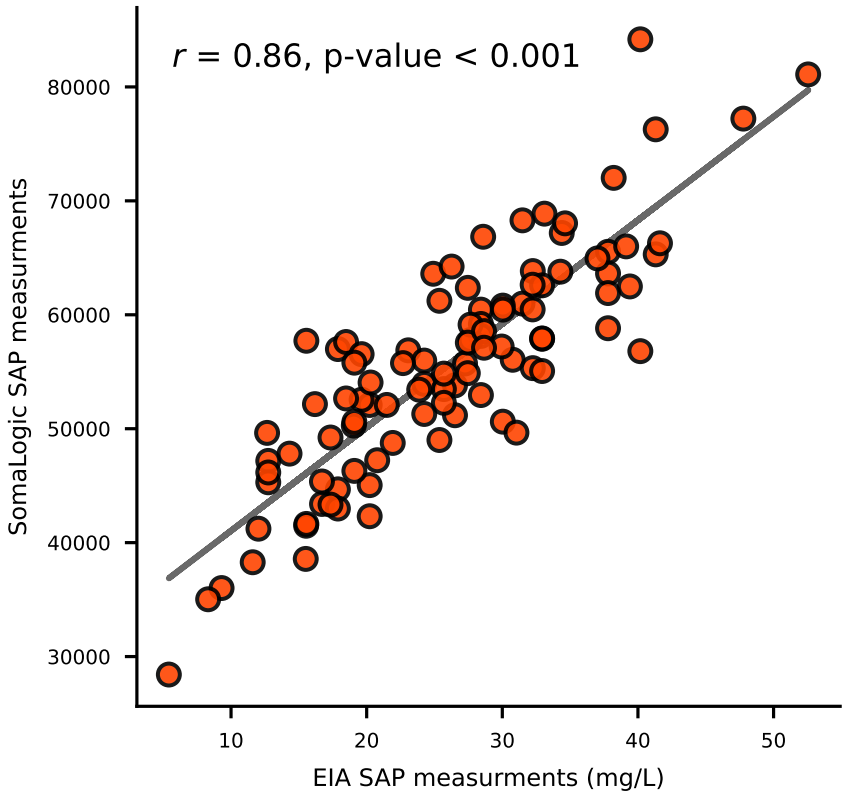
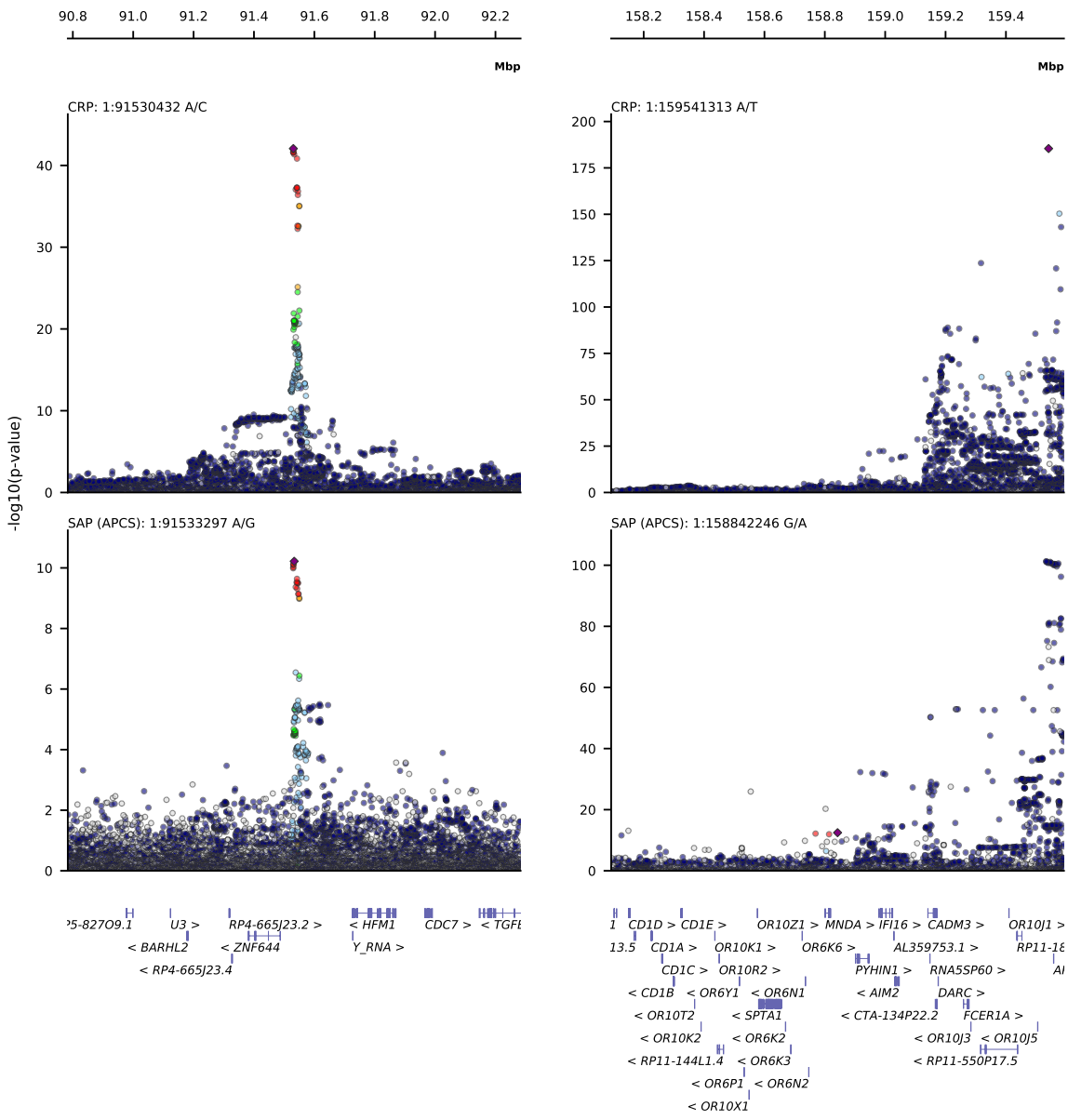


Figure S1: The Pearson correlation estimated in 100 plasma samples from the EPIC-Norfolk study, between SomaLogic relative intensity scores for plasma SAP value and electroimmunoassay (EIA) of actual SAP concentration, standardised and calibrated with authentic, pure, comprehensively characterized, native, human SAP.

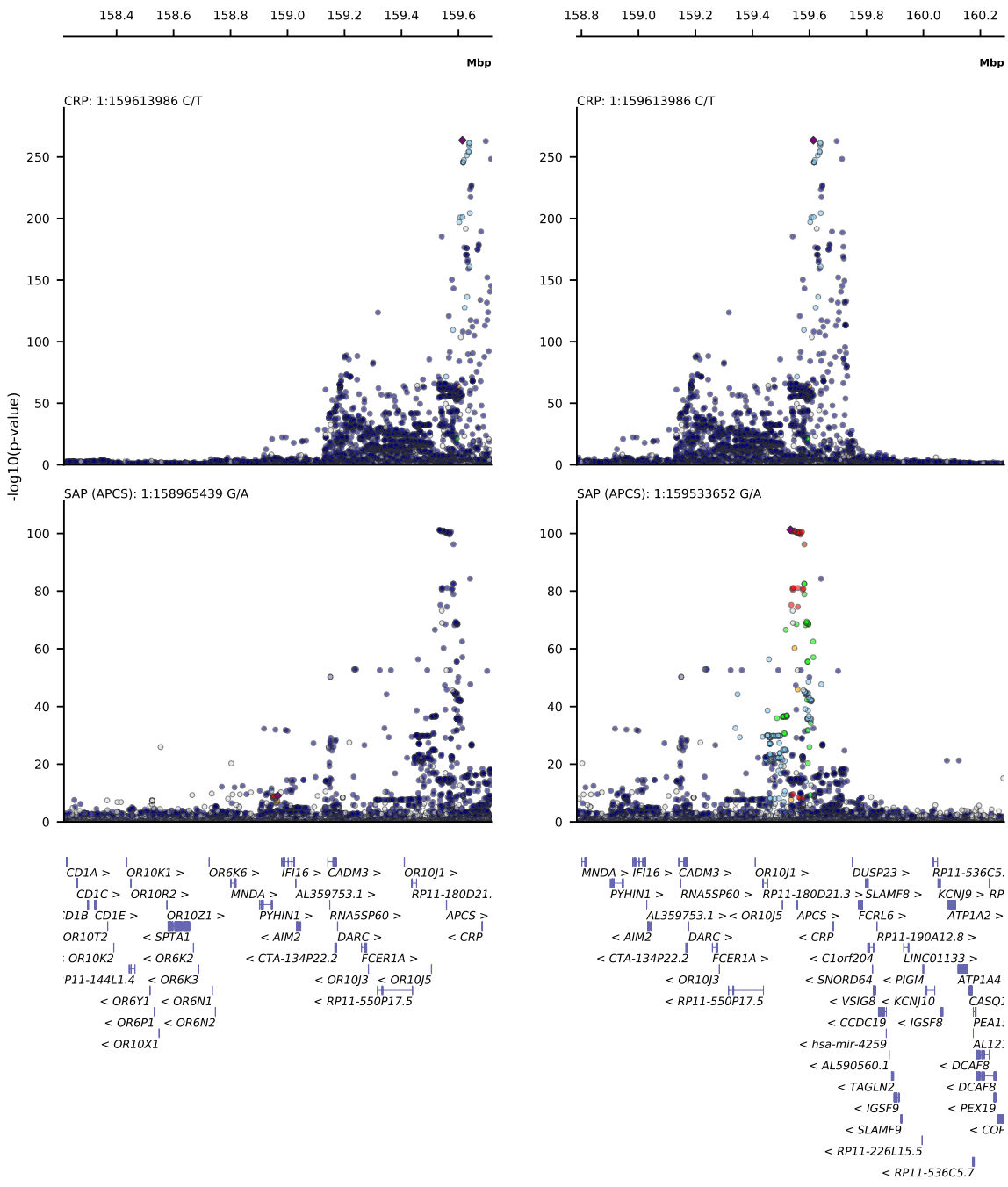
Figure S2:

Locus view plots showing the plasma SAP and CRP signals of the ten independent lead variants identified in the present SAP GWAS meta-analysis of three independent pQTL GWAS based on SomaLogic assays. The variant-specific $-\log_{10}(\text{p-value})$ is plotted (y-axis) against the genomic location (x-axis). The lead variant is indicated by a purple diamond, with linkage disequilibrium (LD) relative to the lead variant indicated by the colours of the dots. The R-squared, representing LD, was from a random sample of 5,000 UK Biobank participants supplemented by the 592 participants of the 1,000 Genomes EUR reference panel.



r^2

≥ 0 ≥ 0.2 ≥ 0.4 ≥ 0.6 ≥ 0.8 no LD lead variant


158.4
158.6
158.8
159.0
159.2
159.4
159.6
Mbp
CRP: 1:159613986 C/T
-log10(p-value)
SAP (APCS): 1:158965439 G/A
CD1A > OR10K1 > OR6K6 > IFI16 > CADM3 > OR10J1 >
CD1C > OR10R2 > MNDA > AL359753.1 > RP11-180D21.
CD1E > OR10Z1 > PYHIN1 > RNA5SP60 > APCS >
OR10T2 < SPTA1 < AIM2 DARC > < CRP
OR10K2 < OR6K2 < CTA-134P22.2 FCER1A >
P11-144L1.4 < OR6K3 < OR10J3 < OR10J5
< OR6Y1 < OR6N1 < RP11-550P17.5
< OR6P1 < OR6N2
< OR10X1
158.8
159.0
159.2
159.4
159.6
159.8
160.0
160.2
Mbp
CRP: 1:159613986 C/T
SAP (APCS): 1:159533652 G/A
MNDA > IFI16 > CADM3 > OR10J1 > DUSP23 > RP11-536C5.
PYHIN1 > RNA5SP60 > RP11-180D21.3 > SLAMF8 > KCNJ9 > RP
AL359753.1 > < OR10J5 APCS > FCRL6 > ATP1A2 >
< AIM2 DARC > < CRP RP11-190A12.8 >
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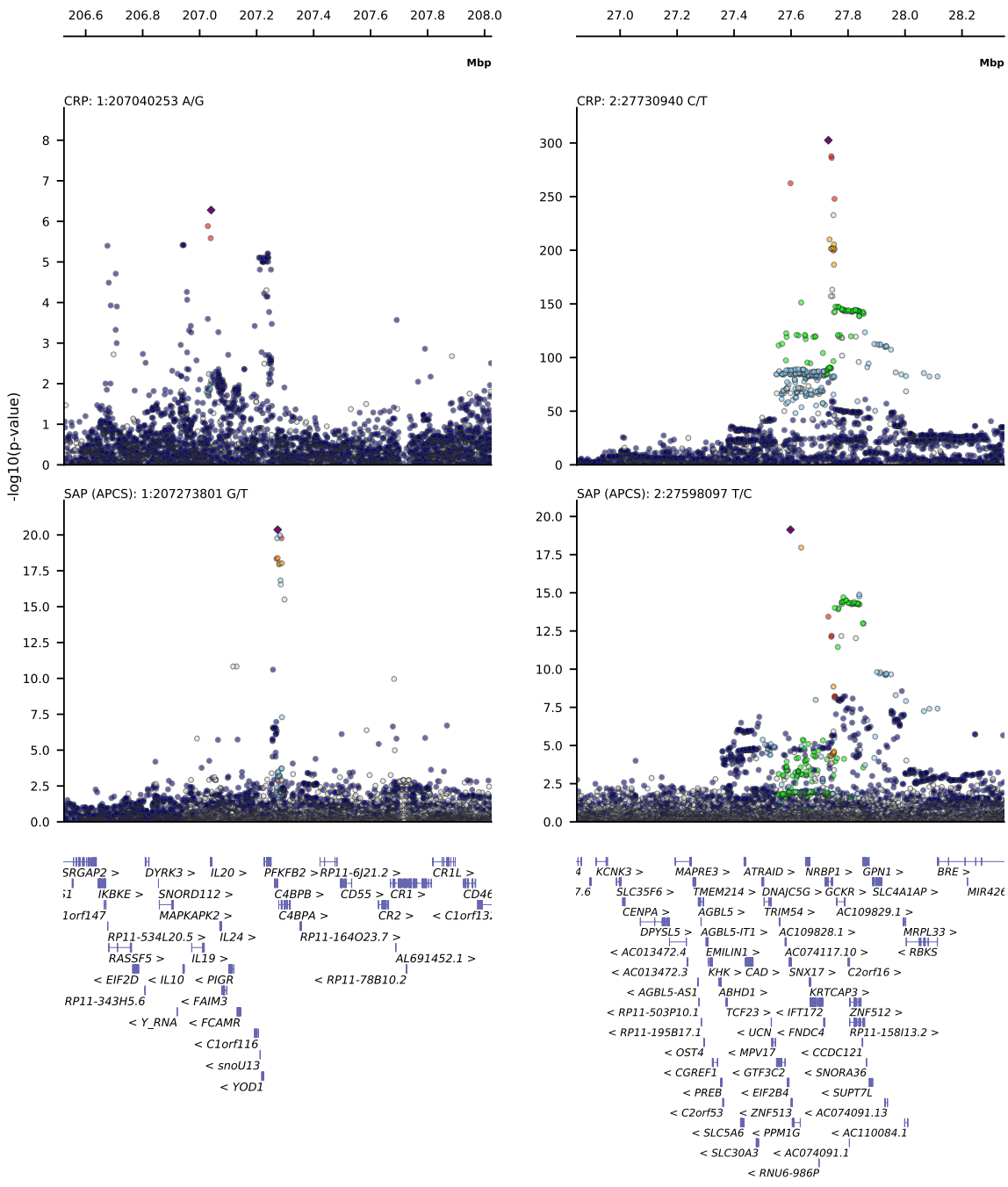
r2
≥ 0
≥ 0.2
≥ 0.4
≥ 0.6
≥ 0.8
no LD
lead variant


206.6
206.8
207.0
207.2
207.4
207.6
207.8
208.0
Mbp
27.0
27.2
27.4
27.6
27.8
28.0
28.2
Mbp
CRP: 1:207040253 A/G
CRP: 2:27730940 C/T
SAP (APCS): 1:207273801 G/T
SAP (APCS): 2:27598097 T/C
-log10(p-value)
SRGAP2 >
DYRK3 >
IL20 >
PFKFB2 >
RP11-6J21.2 >
CR1L >
IKBKE >
SNORD112 >
C4BPB >
CD55 >
CR1 >
MAPKAPK2 >
C4BPA >
CR2 >
RP11-534L20.5 >
IL24 >
RP11-164O23.7 >
RASSF5 >
IL19 >
AL691452.1 >
< EIF2D
< IL10
< PIGR
< RP11-78B10.2
RP11-343H5.6
< FAIM3
< Y_RNA
< FCAMR
< C1orf116
< snoU13
< YOD1
KCNK3 >
MAPRE3 >
ATRAID >
NRBP1 >
GPN1 >
BRE >
SLC35F6 >
TMEM214 >
DNAJC5G >
GCKR >
SLC4A1AP >
CENPA >
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TRIM54 >
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AC074117.10 >
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ZNF512 >
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< FNDC4
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< CCDC121
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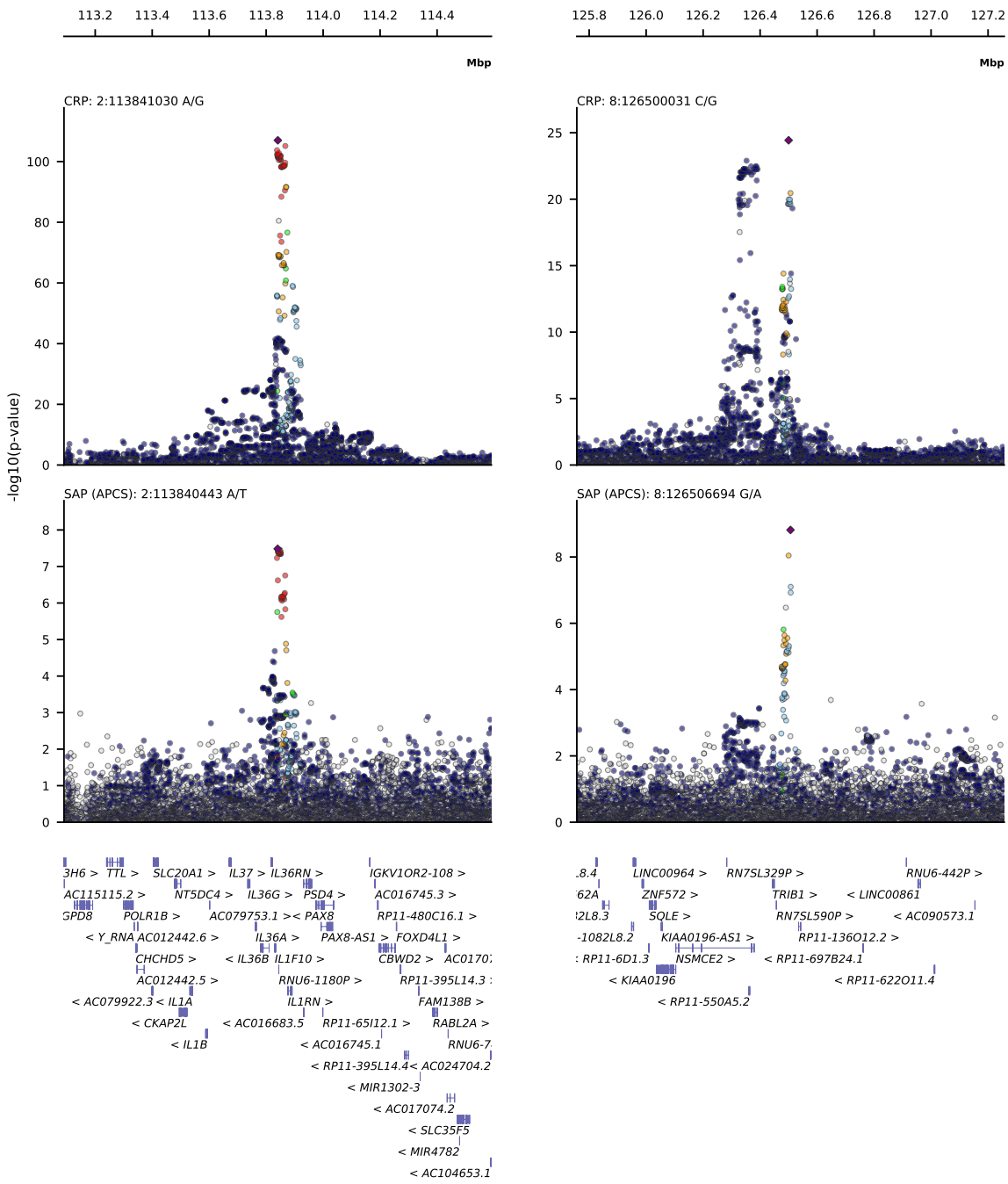
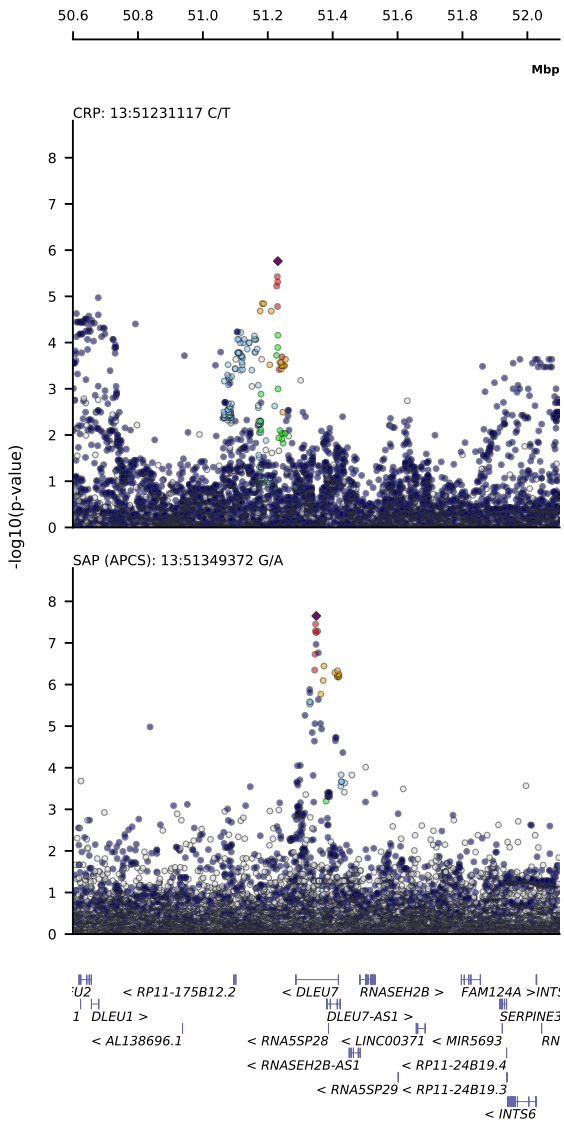
< SNORA36
< PREB
< EIF2B4
< SUPT7L
< C2orf53
< ZNF513
< AC074091.13
< SLC5A6
< PPM1G
< AC110084.1
< SLC30A3
< AC074091.1
< RNU6-986P
r2
≥ 0
≥ 0.2
≥ 0.4
≥ 0.6
≥ 0.8
no LD
lead variant


113.2
113.4
113.6
113.8
114.0
114.2
114.4
Mbp
125.8
126.0
126.2
126.4
126.6
126.8
127.0
127.2
Mbp
CRP: 2:113841030 A/G
CRP: 8:126500031 C/G
-log10(p-value)
SAP (APCS): 2:113840443 A/T
SAP (APCS): 8:126506694 G/A
3H6 > TTL > SLC20A1 > IL37 > IL36RN > IGKV1OR2-108 >
AC115115.2 > NT5DC4 > IL36G > PSD4 > AC016745.3 >
GPD8 POLR1B > AC079753.1 >< PAX8 RP11-480C16.1 >
< Y_RNA AC012442.6 > IL36A > PAX8-AS1 > FOXD4L1 >
CHCHD5 > < IL36B IL1F10 > CBWD2 > AC0170
AC012442.5 > RNU6-1180P > RP11-395L14.3
< AC079922.3 < IL1A IL1RN > FAM138B >
< CKAP2L < AC016683.5 RP11-65I12.1 > RABL2A >
< IL1B < AC016745.1 RNU6-7
< RP11-395L14.4 < AC024704.2
< MIR1302-3
< AC017074.2
< SLC35F5
< MIR4782
< AC104653.1
.8.4 LINC00964 > RN7SL329P > RNU6-442P >
62A ZNF572 > TRIB1 > < LINC00861
2L8.3 SQLE > RN7SL590P > < AC090573.1
-1082L8.2 KIAA0196-AS1 > RP11-136O12.2 >
: RP11-6D1.3 NSMCE2 > < RP11-697B24.1
< KIAA0196 < RP11-622O11.4
< RP11-550A5.2
r2
≥ 0
≥ 0.2
≥ 0.4
≥ 0.6
≥ 0.8
no LD
lead variant



r^2

≥ 0 ≥ 0.2 ≥ 0.4 ≥ 0.6 ≥ 0.8 no LD lead variant

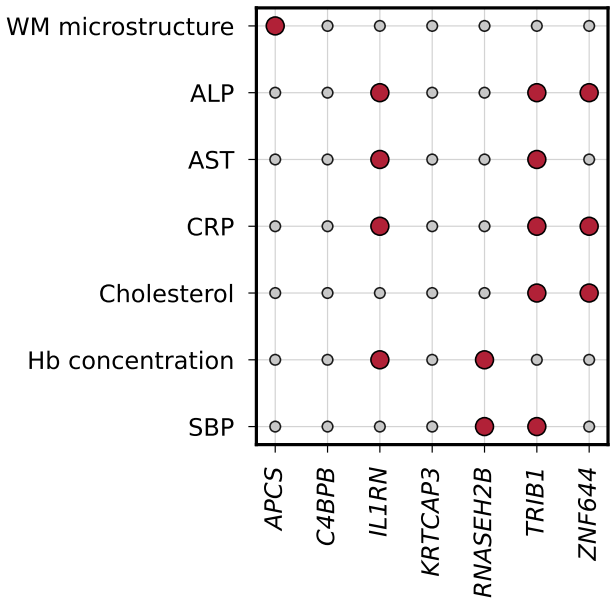


Figure S3: GWAS findings for the 'author assigned genes' reported by GWAS Catalog, showing all traits assigned to *APCS* and traits reported for 2 or more of the trans signals. Abbreviations: WM, white matter; Hb, blood haemoglobin concentration; SBP, systolic blood pressure; plasma concentrations of ALP, alkaline phosphatase; AST, aspartate transaminase; CRP, C-reactive protein. Table S9 shows the complete GWAS Catalog look-up.

Tables

Table S1: Lead variants for plasma serum amyloid P component (SAP) value based on a meta-analysis GWAS in 44,288 subjects. Lead variants from a *trans*-region, defined as a signal beyond +/-2MB with respect to *APCS*, were mapped to putative causal genes using Open Target's 'v2g' pipeline. The provided genetic information is based on genomic build 37.

lead variant (rsid)	chromosome	start position	effect allele	other allele	effect size	standard error	$-\log_{10}$(p-value)	Nearest protein coding gene	Ensembl id (Nearest protein coding gene)	v2g mapped gene	Ensembl id (v2g mapped gene)
rs140308485	1	158842246	A	G	-0.1903	0.0261	12.468	MNDA	ENSG00000163563	APCS	ENSG00000132703
rs13374652	1	158965439	A	G	-0.0892	0.0146	9.045	IFI16	ENSG00000163565	APCS	ENSG00000132703
rs1341664	1	159533652	A	G	-0.2144	0.0100	101.296	APCS	ENSG00000132703	APCS	ENSG00000132703
rs78228389	1	159783225	A	G	0.1335	0.0227	8.382	FCRL6	ENSG00000181036	APCS	ENSG00000132703
rs2808467	1	207273801	G	T	-0.0938	0.0100	20.363	C4BPB	ENSG00000123843	C4BPB	ENSG00000123843
rs165316	1	91533297	A	G	0.0564	0.0086	10.219	ZNF644	ENSG00000122482	ZNF644	ENSG00000122482
rs10188292	2	113840443	A	T	-0.0395	0.0071	7.484	IL1F10	ENSG00000136697	IL1RN	ENSG00000136689
rs4665972	2	27598097	C	T	-0.0807	0.0088	19.132	SNX17	ENSG00000115234	KRTCAP3	ENSG00000157992
rs112875651	8	126506694	A	G	-0.0443	0.0073	8.815	TRIB1	ENSG00000173334	TRIB1	ENSG00000173334
rs9591359	13	51349372	A	G	-0.0517	0.0092	7.650	DLEU1	ENSG00000176124	RNASEH2B	ENSG00000136104

Table S2: SAP lead variant associations with plasma concentration of C-reactive protein (ref: 62)

lead variant (rsid)	chromosome	start position	effect allele	other allele	effect size	standard error	$-\log_{10}$(p-value)
rs140308485	1	158842246	A	G	-0.0150	0.0081	1.1836
rs13374652	1	158965439	A	G	0.0005	0.0043	0.0424
rs1341664	1	159533652	A	G	-0.0153	0.0031	6.2623
rs78228389	1	159783225	A	G	-0.0242	0.0058	4.5163
rs2808467	1	207273801	G	T	-0.0028	0.0027	0.5109
rs165316	1	91533297	A	G	0.0346	0.0025	41.3587
rs10188292	2	113840443	A	T	-0.0439	0.0020	102.3605
rs4665972	2	27598097	C	T	-0.0741	0.0021	262.4584
rs112875651	8	126506694	A	G	-0.0202	0.0021	20.4605
rs9591359	13	51349372	A	G	-0.0017	0.0026	0.2834

Table S3: Open target v2g results mapping *trans*-variant rs2808467 to a putative causal gene

Gene	Overall V2G	Distance (Canonical TSS)	pQTL	sQTL	eQTL	Enhancer-TSS corr (FANTOM5)	PCHi-C (Javierre, 2016)	DHS-promoter corr (Thurman, 2012)	PCHi-C (Jung, 2019)	VEP (Ensembl)
YOD1	0.0598	47476	-	-	-	-	-	-	-	-
CD55	0.1793	221063	-	-	0.6	-	0.9	-	-	-
PIGR	0.0465	153990	-	-	-	-	-	-	-	-
IL20	0.0332	234833	-	-	-	-	-	-	-	-
DYRK3	0.0066	464920	-	-	-	-	-	-	-	-
MAPKAPK2	0.0133	415551	-	-	-	-	-	-	-	-
C4BPA	0.1992	3777	-	-	1	-	-	-	-	-
EIF2D	0.0000	487991	-	-	-	-	-	-	-	-
IL24	0.0398	203013	-	-	-	-	-	-	-	-
IL19	0.0199	329692	-	-	-	-	-	-	-	-
FCMR	0.0398	177209	-	-	-	-	-	-	-	-
C1orf116	0.0598	67700	-	-	-	-	-	-	-	-
C4BPB	0.2676	11596	-	1	-	-	-	-	-	-
CD46	0.0000	-	-	0	-	-	-	-	-	-
IL10	0.0199	325915	-	-	-	-	-	-	-	-
CR1	0.0598	395691	-	-	-	-	0.7	-	-	-
PFKFB2	0.0598	66090	-	-	-	-	-	-	-	-
FCAMR	0.0465	129831	-	-	-	-	-	-	-	-
CR2	0.0531	352568	-	-	-	-	0.5	-	-	-

General:
Entries without information are marked by '-'.

Table S4: Open target v2g results mapping *trans*-variant rs165316 to a putative causal gene

Gene	Overall V2G	Distance (Canonical TSS)	pQTL	sQTL	eQTL	Enhancer-TSS corr (FANTOM5)	PCHi-C (Javierre, 2016)	DHS-promoter corr (Thurman, 2012)	PCHi-C (Jung, 2019)	VEP (Ensembl)
ZNF644	0.0598	45468	-	-	-	-	-	-	-	-
BARHL2	0.0199	350438	-	-	-	-	-	-	-	-
CDC7	0.0066	433111	-	-	-	-	-	-	-	-
HFM1	0.0199	337116	-	-	-	-	-	-	-	-

General:
Entries without information are marked by '-'.

Table S5: Open target v2g results mapping *trans*-variant rs10188292 to a putative causal gene

Gene	Overall V2G	Distance (Canonical TSS)	pQTL	sQTL	eQTL	Enhancer-TSS corr (FANTOM5)	PCHi-C (Javierre, 2016)	DHS-promoter corr (Thurman, 2012)	PCHi-C (Jung, 2019)	VEP (Ensembl)
IL37	0.0465	171701	-	-	-	-	-	-	-	-
CBWD2	0.0199	354825	-	-	-	-	-	-	-	-
PAX8	0.0996	196055	-	-	-	-	0.9	-	-	-
IL1F10	0.0930	14896	-	-	0.2	-	-	-	-	-
IGKV1OR2-108	0.0266	323530	-	-	-	-	-	-	-	-
IL36G	0.0531	109663	-	-	-	-	-	-	-	-
FOXD4L1	0.0133	415799	-	-	-	-	-	-	-	-
CHCHD5	0.0000	498626	-	-	-	-	-	-	-	-
IL1B	0.0332	246050	-	-	-	-	-	-	-	-
IL36A	0.0531	77407	-	-	-	-	-	-	-	-
CKAP2L	0.0266	318202	-	-	-	-	-	-	-	-
IL1A	0.0266	298373	-	-	-	-	-	-	-	-
IL36RN	0.0664	24228	-	-	-	-	-	-	0	-
SLC20A1	0.0465	436927	-	-	0.3	-	-	-	-	-
PSD4	0.2058	74459	-	-	0.7	-	0.8	-	0	-
IL36B	0.0598	29999	-	-	-	-	-	-	0	-
IL1RN	0.4058	16449	0.9	0.4	0.6	-	0.9	-	-	-
NT5DC4	0.0199	361846	-	-	-	-	-	-	-	-

General:
Entries without information are marked by '-'.

Table S6: Open target v2g results mapping *trans*-variant rs4665972 to a putative causal gene

Gene	Overall V2G	Distance (Canonical TSS)	pQTL	sQTL	eQTL	Enhancer-TSS corr (FANTOM5)	PCHi-C (Javierre, 2016)	DHS-promoter corr (Thurman, 2012)	PCHi-C (Jung, 2019)	VEP (Ensembl)
DNAJC5G	0.0531	99797	-	-	-	-	-	-	-	-
PREB	0.0332	240564	-	-	-	-	-	-	-	-
KHK	0.0398	288483	-	-	-	-	0.2	-	-	-
TRIM54	0.1738	92801	-	0.6	-	-	-	-	-	-
MAPRE3	0.0133	404593	-	-	-	-	-	-	-	-
GTF3C2	0.1328	18231	-	-	-	-	1	-	-	-
KRTCAP3	0.2799	67136	-	0.5	0.9	-	-	-	-	-
SNX17	0.1994	4734	-	-	0.8	-	0.1	-	-	intron_variant
ZNF512	0.0398	207739	-	-	-	-	-	-	-	-
GPN1	0.1531	253017	-	0.2	0.6	-	0	-	-	-
EIF2B4	0.1262	4892	-	-	0.4	-	0.1	-	-	-
PPM1G	0.1527	34361	-	-	0.7	-	-	-	-	-
IFT172	0.2475	114575	-	0.9	0.1	-	-	-	-	-
ZNF513	0.1062	5560	-	-	0.3	-	-	-	-	-
NRBP1	0.1793	52560	-	-	0.9	-	-	-	-	-
TMEM214	0.0664	342320	-	-	-	-	0.7	-	-	-
SLC4A1AP	0.0465	288196	-	-	-	-	0.3	-	-	-
CGREF1	0.0332	256102	-	-	-	-	-	-	-	-
FNDC4	0.2736	119970	-	0.7	0.6	-	-	-	-	-
ABHD1	0.0332	251441	-	-	-	-	-	-	-	-
C2orf16	0.0465	162156	-	-	-	-	-	-	-	-
SLC30A3	0.0531	99413	-	-	-	-	-	-	-	-
MRPL33	0.0133	396487	-	-	-	-	-	-	-	-
AGBL5	0.0199	332866	-	-	-	-	-	-	-	-
SLC5A6	0.1728	162272	-	0.1	0.8	-	-	-	-	-
TCF23	0.0332	226226	-	-	-	-	-	-	-	-
OST4	0.0266	303576	-	-	-	-	0	-	-	-
ATRAID	0.1527	163189	-	-	0.8	-	-	-	-	-
UCN	0.0598	66785	-	-	-	-	-	-	-	-
CCDC121	0.0332	253782	-	-	-	-	0	-	-	-
PRR30	0.0332	235820	-	-	-	-	-	-	-	-
SUPT7L	0.0465	288610	-	-	-	-	0.3	-	-	-
EMILIN1	0.0398	296615	-	-	-	-	0.2	-	-	-
CAD	0.0465	157861	-	-	-	-	-	-	-	-
MPV17	0.0598	49550	-	-	-	-	-	-	-	-
GCKR	0.2133	121609	-	0.4	0.6	-	-	-	-	-

General:
Entries without information are marked by '-'.

Table S7: Open target v2g results mapping *trans*-variant rs112875651 to a putative causal gene

Gene	Overall V2G	Distance (Canonical TSS)	pQTL	sQTL	eQTL	Enhancer-TSS corr (FANTOM5)	PCHi-C (Javierre, 2016)	DHS-promoter corr (Thurman, 2012)	PCHi-C (Jung, 2019)	VEP (Ensembl)
SQLE	0.0000	495955	-	-	-	-	-	-	-	-
TRIB1	0.0598	64094	-	-	-	-	-	-	-	-
WASHC5	0.0398	402633	-	-	-	-	0.4	-	-	-
NSMCE2	0.0398	402773	-	-	-	-	0.4	-	-	-

General:
Entries without information are marked by '-'.

Table S8: Open target v2g results mapping *trans*-variant rs9591359 to a putative causal gene

Gene	Overall V2G	Distance (Canonical TSS)	pQTL	sQTL	eQTL	Enhancer-TSS corr (FANTOM5)	PCHi-C (Javierre, 2016)	DHS-promoter corr (Thurman, 2012)	PCHi-C (Jung, 2019)	VEP (Ensembl)
DLEU7	0.0799	68703	-	-	-	-	-	-	-	intron_variant
C13orf42	0.0066	425016	-	-	-	-	-	-	-	-
RNASEH2B	0.0863	134511	-	-	0.3	-	-	-	0	-
FAM124A	0.0066	447098	-	-	-	-	-	-	-	-

General:
Entries without information are marked by '-'.

Table S9: GWAS Catalog look-ups for putative causal genes for plasma SAP value.

Trait	APCS	C4BPB	IL1RN	KRTCAP3	RNASEH2B	TRIB1	ZNF644	Counts
AAA	0	0	0	0	0	1	0	1
ALP	0	0	1	0	0	1	1	3
ALT	0	0	0	0	0	1	0	1
AST	0	0	1	0	0	1	0	2
Adiponectin	0	0	0	0	0	1	0	1
Albuminuria	0	0	0	0	0	1	0	1
Alcohol consumption	0	0	0	0	0	1	0	1
Apo-A1	0	0	0	0	0	1	0	1
Apo-B	0	0	0	0	0	1	0	1
BMI	0	0	0	0	0	1	0	1
BPH	0	0	0	0	1	0	0	1
Body height	0	0	0	0	0	1	0	1
CRP	0	0	1	0	0	1	1	3
Cholesterol	0	0	0	0	0	1	1	2
Ferritin	0	0	0	0	0	1	0	1
Fibrinogen	0	0	1	0	0	0	0	1
GGT	0	0	0	0	0	1	0	1
Glycine	0	0	0	0	0	1	0	1
Granulocytes	0	0	1	0	0	0	0	1
HDL-C	0	0	0	0	0	1	0	1
Hb concentration	0	0	1	0	1	0	0	2
HbA1c	0	0	0	0	0	1	0	1
IBD	0	0	0	0	0	1	0	1
IL6 concentration	0	0	1	0	0	0	0	1
Intelligence	0	0	0	0	0	0	1	1
LDL-C	0	0	0	0	0	1	0	1
Lymphocytes	0	0	1	0	0	0	0	1
Metabolic syndrome	0	0	0	0	0	1	0	1
Monocytes	0	0	1	0	0	0	0	1
Neutrophils	0	0	1	0	0	0	0	1
RDW	0	0	1	0	0	0	0	1
SBP	0	0	0	0	1	1	0	2
T2DM	0	0	0	0	0	1	0	1
UTI	0	0	0	0	1	0	0	1
Urate	0	0	0	0	0	0	1	1
Urine alb/creat	0	0	0	0	0	1	0	1
WM microstructure	1	0	0	0	0	0	0	1
eGFR	0	0	0	0	0	1	0	1

Table S10: The *cis*-Mendelian randomization results for the effects of one standard deviation higher plasma SAP value or plasma CRP concentration on dementia outcomes.

GWAS pQTL	Exposure (unit)	Outcome trait	Point estimate (95%CI)	No variants	model	Heterogeneity p-value	Heterogeneity chi-square statistic	p-value (scientific notation)	Unit	Multiplicity threshold
Interval (n: 3,301)	SAP (SD)	Alzheimer's disease	1.08 (1.03; 1.14)	11	IVW	0.0443	18.698	3.5×10^{-3}	OR	0.0028
AGES (n: 5,368)	SAP (SD)	Alzheimer's disease	1.19 (1.07; 1.33)	28	MR Egger	0.0143	44.212	1.4×10^{-3}	OR	0.0028
DECODE (n: 35,559)	SAP (SD)	Alzheimer's disease	1.05 (1.00; 1.10)	58	IVW	0.0009	96.355	6.1×10^{-2}	OR	0.0028
Combined SL (n: 44,288)	SAP (SD)	Alzheimer's disease	1.07 (1.02; 1.11)	53	IVW	0.0002	96.500	1.8×10^{-3}	OR	0.0028
CRP (n: 575,531)	CRP (SD)	Alzheimer's disease	1.04 (0.94; 1.16)	132	MR Egger	0.0013	183.930	4.7×10^{-1}	OR	0.0028
Interval (n: 3,301)	SAP (SD)	Lewy body dementia	1.57 (1.16; 2.12)	12	MR Egger	0.4782	9.579	3.1×10^{-3}	OR	0.0028
AGES (n: 5,368)	SAP (SD)	Lewy body dementia	1.27 (0.94; 1.72)	25	MR Egger	0.1004	31.986	1.2×10^{-1}	OR	0.0028
DECODE (n: 35,559)	SAP (SD)	Lewy body dementia	0.91 (0.73; 1.14)	52	MR Egger	0.3687	52.737	4.2×10^{-1}	OR	0.0028
Combined SL (n: 44,288)	SAP (SD)	Lewy body dementia	1.37 (1.19; 1.59)	45	IVW	0.3367	47.374	1.5×10^{-5}	OR	0.0028
CRP (n: 575,531)	CRP (SD)	Lewy body dementia	0.82 (0.63; 1.06)	127	MR Egger	0.0000	226.145	1.2×10^{-1}	OR	0.0028

General:
Studies: Interval (ref: 24), DECODE (ref: 25), AGES (ref: 26), Combined SL, total subjects in the three GWAS with SomaLogic values for SAP.

Table S11: The *cis*-Mendelian randomization results for the effects of one standard deviation higher plasma SAP value on secondary outcomes

GWAS pQTL	Exposure (unit)	Outcome trait	Point estimate (95%CI)	No variants	model	Heterogeneity p-value	Heterogeneity chi-square statistic	p-value (scientific notation)	Unit	Multiplicity threshold
Interval (n: 3,301)	SAP (SD)	Osteoarthritis	1.07 (1.03; 1.12)	13	MR Egger	0.0049	26.819	8.6×10^{-4}	OR	0.0028
AGES (n: 5,368)	SAP (SD)	Osteoarthritis	1.01 (1.00; 1.03)	27	IVW	0.1545	33.267	1.3×10^{-1}	OR	0.0028
DECODE (n: 35,559)	SAP (SD)	Osteoarthritis	1.09 (1.06; 1.12)	58	MR Egger	0.0000	115.978	8.0×10^{-9}	OR	0.0028
Combined SL (n: 44,288)	SAP (SD)	Osteoarthritis	1.01 (1.00; 1.03)	49	IVW	0.0127	72.505	1.2×10^{-1}	OR	0.0028
Interval (n: 3,301)	SAP (SD)	Osteoarthritis (hip)	1.13 (1.04; 1.24)	13	MR Egger	0.9109	5.389	5.4×10^{-3}	OR	0.0028
AGES (n: 5,368)	SAP (SD)	Osteoarthritis (hip)	1.11 (1.01; 1.23)	28	MR Egger	0.1388	33.851	2.6×10^{-2}	OR	0.0028
DECODE (n: 35,559)	SAP (SD)	Osteoarthritis (hip)	1.01 (0.97; 1.05)	59	IVW	0.0014	95.624	6.6×10^{-1}	OR	0.0028
Combined SL (n: 44,288)	SAP (SD)	Osteoarthritis (hip)	1.09 (1.02; 1.17)	55	MR Egger	0.1155	65.550	1.2×10^{-2}	OR	0.0028
Interval (n: 3,301)	SAP (SD)	Osteoarthritis (hip and knee)	1.12 (1.04; 1.21)	12	MR Egger	0.0552	17.984	3.6×10^{-3}	OR	0.0028
AGES (n: 5,368)	SAP (SD)	Osteoarthritis (hip and knee)	1.02 (1.00; 1.04)	27	IVW	0.0000	73.906	6.5×10^{-2}	OR	0.0028
DECODE (n: 35,559)	SAP (SD)	Osteoarthritis (hip and knee)	1.10 (1.05; 1.15)	53	MR Egger	0.0061	79.838	8.5×10^{-6}	OR	0.0028
Combined SL (n: 44,288)	SAP (SD)	Osteoarthritis (hip and knee)	1.00 (0.97; 1.02)	51	IVW	0.0000	111.507	9.2×10^{-1}	OR	0.0028
Interval (n: 3,301)	SAP (SD)	Osteoarthritis (knee)	1.14 (1.04; 1.24)	12	MR Egger	0.0692	17.242	6.3×10^{-3}	OR	0.0028
AGES (n: 5,368)	SAP (SD)	Osteoarthritis (knee)	1.15 (1.08; 1.24)	26	MR Egger	0.0005	53.489	6.1×10^{-5}	OR	0.0028
DECODE (n: 35,559)	SAP (SD)	Osteoarthritis (knee)	1.09 (1.04; 1.15)	55	MR Egger	0.0077	81.160	6.8×10^{-4}	OR	0.0028
Combined SL (n: 44,288)	SAP (SD)	Osteoarthritis (knee)	0.97 (0.94; 1.00)	49	IVW	0.0000	103.149	4.8×10^{-2}	OR	0.0028
Interval (n: 3,301)	SAP (SD)	SLE	0.94 (0.78; 1.13)	10	IVW	0.0818	15.350	4.8×10^{-1}	OR	0.0028
AGES (n: 5,368)	SAP (SD)	SLE	0.91 (0.83; 0.99)	26	IVW	0.0257	40.531	2.7×10^{-2}	OR	0.0028
DECODE (n: 35,559)	SAP (SD)	SLE	0.93 (0.83; 1.04)	49	IVW	0.0051	76.845	2.0×10^{-1}	OR	0.0028
Combined SL (n: 44,288)	SAP (SD)	SLE	0.93 (0.85; 1.01)	45	IVW	0.0015	77.066	9.5×10^{-2}	OR	0.0028
Interval (n: 3,301)	SAP (SD)	IPF	1.00 (1.00; 1.00)	13	IVW	0.0296	22.785	2.1×10^{-3}	OR	0.0028
AGES (n: 5,368)	SAP (SD)	IPF	1.00 (1.00; 1.00)	28	MR Egger	0.5940	23.684	2.1×10^{-1}	OR	0.0028
DECODE (n: 35,559)	SAP (SD)	IPF	1.00 (1.00; 1.00)	58	MR Egger	0.0959	70.213	1.9×10^{-1}	OR	0.0028
Combined SL (n: 44,288)	SAP (SD)	IPF	1.00 (1.00; 1.00)	52	IVW	0.0035	82.371	7.1×10^{-1}	OR	0.0028
Interval (n: 3,301)	SAP (SD)	SBP	-0.03 (-0.16; 0.11)	10	IVW	0.3014	10.637	7.0×10^{-1}	mmHg	0.0028
AGES (n: 5,368)	SAP (SD)	SBP	-0.08 (-0.33; 0.18)	27	MR Egger	0.1258	33.212	5.5×10^{-1}	mmHg	0.0028
DECODE (n: 35,559)	SAP (SD)	SBP	-0.21 (-0.47; 0.06)	41	MR Egger	0.1069	50.255	1.3×10^{-1}	mmHg	0.0028
Combined SL (n: 44,288)	SAP (SD)	SBP	-0.16 (-0.26; -0.07)	46	IVW	0.0005	82.593	1.1×10^{-3}	mmHg	0.0028
Interval (n: 3,301)	SAP (SD)	DBP	-0.55 (-1.13; 0.04)	10	MR Egger	0.0763	14.214	6.7×10^{-2}	mmHg	0.0028
AGES (n: 5,368)	SAP (SD)	DBP	-0.04 (-0.10; 0.01)	28	IVW	0.0044	50.121	1.2×10^{-1}	mmHg	0.0028
DECODE (n: 35,559)	SAP (SD)	DBP	0.03 (-0.04; 0.11)	46	IVW	0.0001	88.512	3.9×10^{-1}	mmHg	0.0028
Combined SL (n: 44,288)	SAP (SD)	DBP	-0.09 (-0.15; -0.03)	44	IVW	0.0002	84.341	2.2×10^{-3}	mmHg	0.0028
Interval (n: 3,301)	SAP (SD)	CHD	1.03 (1.01; 1.05)	13	IVW	0.7922	7.909	3.5×10^{-4}	OR	0.0028
AGES (n: 5,368)	SAP (SD)	CHD	1.01 (0.97; 1.05)	26	MR Egger	0.0000	62.829	7.6×10^{-1}	OR	0.0028
DECODE (n: 35,559)	SAP (SD)	CHD	0.99 (0.97; 1.01)	54	IVW	0.0011	90.282	3.1×10^{-1}	OR	0.0028
Combined SL (n: 44,288)	SAP (SD)	CHD	1.03 (1.01; 1.05)	50	IVW	0.0044	78.772	7.3×10^{-4}	OR	0.0028
Interval (n: 3,301)	SAP (SD)	T2DM	1.02 (1.00; 1.05)	10	IVW	0.0131	20.896	8.8×10^{-2}	OR	0.0028
AGES (n: 5,368)	SAP (SD)	T2DM	1.02 (1.00; 1.04)	26	IVW	0.0126	43.401	3.6×10^{-2}	OR	0.0028
DECODE (n: 35,559)	SAP (SD)	T2DM	0.96 (0.92; 1.00)	50	MR Egger	0.0208	69.981	5.1×10^{-2}	OR	0.0028
Combined SL (n: 44,288)	SAP (SD)	T2DM	1.01 (0.98; 1.03)	49	IVW	0.0306	67.935	6.0×10^{-1}	OR	0.0028
Interval (n: 3,301)	SAP (SD)	ALT	0.00 (-0.00; 0.01)	13	MR Egger	0.2146	14.343	9.9×10^{-2}	log(U/L)	0.0028
AGES (n: 5,368)	SAP (SD)	ALT	0.00 (-0.00; 0.00)	29	IVW	0.2893	31.643	6.7×10^{-1}	log(U/L)	0.0028
DECODE (n: 35,559)	SAP (SD)	ALT	-0.00 (-0.00; 0.00)	57	MR Egger	0.8466	44.375	7.7×10^{-1}	log(U/L)	0.0028
Combined SL (n: 44,288)	SAP (SD)	ALT	0.00 (-0.00; 0.00)	52	IVW	0.1701	60.510	1.9×10^{-1}	log(U/L)	0.0028
Interval (n: 3,301)	SAP (SD)	AST	-0.00 (-0.02; 0.01)	7	IVW	0.8304	2.825	5.5×10^{-1}	SD	0.0028
AGES (n: 5,368)	SAP (SD)	AST	-0.00 (-0.01; 0.01)	16	IVW	0.3593	16.348	9.8×10^{-1}	SD	0.0028
DECODE (n: 35,559)	SAP (SD)	AST	-0.02 (-0.04; 0.00)	30	MR Egger	0.0023	53.883	7.7×10^{-2}	SD	0.0028
Combined SL (n: 44,288)	SAP (SD)	AST	-0.00 (-0.01; 0.00)	30	IVW	0.0020	55.860	1.4×10^{-1}	SD	0.0028

Interval (n: 3,301)	SAP (SD)	GGT	0.00 (-0.00; 0.00)	13	IVW	0.0060	27.737	6.0×10^{-2}	log(U/L)	0.0028
AGES (n: 5,368)	SAP (SD)	GGT	-0.00 (-0.00; 0.00)	28	IVW	0.0129	45.937	8.8×10^{-1}	log(U/L)	0.0028
DECODE (n: 35,559)	SAP (SD)	GGT	0.00 (0.00; 0.00)	58	IVW	0.0001	107.573	1.5×10^{-2}	log(U/L)	0.0028
Combined SL (n: 44,288)	SAP (SD)	GGT	0.00 (0.00; 0.01)	52	MR Egger	0.0002	93.710	5.0×10^{-2}	log(U/L)	0.0028
Interval (n: 3,301)	SAP (SD)	Total brain volume	0.01 (-0.02; 0.04)	11	IVW	0.7042	7.223	6.3×10^{-1}	SD	0.0028
AGES (n: 5,368)	SAP (SD)	Total brain volume	0.01 (-0.01; 0.03)	30	IVW	0.5319	27.739	1.7×10^{-1}	SD	0.0028
DECODE (n: 35,559)	SAP (SD)	Total brain volume	-0.01 (-0.04; 0.02)	50	IVW	0.8835	37.548	5.7×10^{-1}	SD	0.0028
Combined SL (n: 44,288)	SAP (SD)	Total brain volume	0.06 (0.02; 0.10)	50	MR Egger	0.3700	50.634	2.0×10^{-3}	SD	0.0028
Interval (n: 3,301)	SAP (SD)	Cerebral WMH volume	-0.08 (-0.14; -0.03)	10	IVW	0.3732	9.725	2.2×10^{-3}	white	0.0028
AGES (n: 5,368)	SAP (SD)	Cerebral WMH volume	-0.12 (-0.20; -0.04)	29	MR Egger	0.6213	24.162	4.3×10^{-3}	white	0.0028
DECODE (n: 35,559)	SAP (SD)	Cerebral WMH volume	-0.06 (-0.10; -0.02)	55	IVW	0.0238	76.467	3.9×10^{-3}	white	0.0028
Combined SL (n: 44,288)	SAP (SD)	Cerebral WMH volume	-0.03 (-0.07; 0.01)	52	IVW	0.0411	69.816	1.4×10^{-1}	white	0.0028
Interval (n: 3,301)	SAP (SD)	Circulating total tau	0.03 (-0.00; 0.06)	11	IVW	0.0299	19.935	6.6×10^{-2}	log2	0.0028
AGES (n: 5,368)	SAP (SD)	Circulating total tau	-0.02 (-0.04; 0.01)	27	IVW	0.1325	34.101	1.7×10^{-1}	log2	0.0028
DECODE (n: 35,559)	SAP (SD)	Circulating total tau	0.05 (0.02; 0.08)	53	IVW	0.0141	76.877	3.6×10^{-3}	log2	0.0028
Combined SL (n: 44,288)	SAP (SD)	Circulating total tau	-0.09 (-0.16; -0.02)	49	MR Egger	0.0126	71.314	1.8×10^{-2}	log2	0.0028

General:

Studies: Interval (ref: 24), DECODE (ref: 25), AGES (ref: 26), Combined SL, total subjects in the three GWAS with SomaLogic values for SAP. Outcome trait abbreviations: SLE, systemic lupus erythematosus; IPF, idiopathic pulmonary fibrosis, SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; T2DM, type 2 diabetes mellitus; ALT, AST, GGT, plasma concentrations of, respectively, alanine transaminase, aspartate transaminase, γ-glutamyl transferase; cerebral WMH, white matter hyperintensity, volume.

Table S12: The *cis*-Mendelian randomization results for the effects of one standard deviation higher plasma CRP concentration on secondary outcomes

GWAS pQTL	Exposure (unit)	Outcome trait	Point estimate (95%CI)	No variants	model	Heterogeneity p-value	Heterogeneity chi-square statistic	p-value (scientific notation)	Unit	Multiplicity threshold
CRP (n: 575,531)	CRP (SD)	Osteoarthritis	1.04 (1.00; 1.08)	153	MR Egger	0.0000	251.92	2.9×10^{-2}	OR	0.0028
CRP (n: 575,531)	CRP (SD)	Osteoarthritis (hip)	1.15 (1.08; 1.23)	172	MR Egger	0.0000	258.36	2.3×10^{-5}	OR	0.0028
CRP (n: 575,531)	CRP (SD)	Osteoarthritis (hip and knee)	1.02 (0.98; 1.07)	158	MR Egger	0.0000	321.26	3.4×10^{-1}	OR	0.0028
CRP (n: 575,531)	CRP (SD)	Osteoarthritis (knee)	0.99 (0.94; 1.05)	165	MR Egger	0.0000	316.49	8.0×10^{-1}	OR	0.0028
CRP (n: 575,531)	CRP (SD)	SLE	0.77 (0.62; 0.95)	110	MR Egger	0.0000	204.75	1.4×10^{-2}	OR	0.0028
CRP (n: 575,531)	CRP (SD)	IPF	1.00 (1.00; 1.00)	166	MR Egger	0.0000	323.75	8.4×10^{-2}	OR	0.0028
CRP (n: 575,531)	CRP (SD)	SBP	-0.05 (-0.20; 0.11)	102	IVW	0.0000	180.05	5.5×10^{-1}	mmHg	0.0028
CRP (n: 575,531)	CRP (SD)	DBP	0.05 (-0.05; 0.15)	105	IVW	0.0000	182.27	2.9×10^{-1}	mmHg	0.0028
CRP (n: 575,531)	CRP (SD)	CHD	1.02 (0.99; 1.05)	151	MR Egger	0.0000	241.24	2.2×10^{-1}	OR	0.0028
CRP (n: 575,531)	CRP (SD)	T2DM	1.03 (0.99; 1.07)	140	MR Egger	0.0000	235.82	1.5×10^{-1}	OR	0.0028
CRP (n: 575,531)	CRP (SD)	ALT	0.01 (0.00; 0.01)	165	IVW	0.0000	340.31	4.1×10^{-8}	log(U/L)	0.0028
CRP (n: 575,531)	CRP (SD)	AST	0.02 (0.01; 0.03)	50	IVW	0.0010	85.16	3.3×10^{-4}	SD	0.0028
CRP (n: 575,531)	CRP (SD)	GGT	-0.00 (-0.00; 0.00)	156	IVW	0.0000	284.49	8.5×10^{-1}	log(U/L)	0.0028
CRP (n: 575,531)	CRP (SD)	Total brain volume	0.04 (0.00; 0.08)	122	MR Egger	0.0001	187.06	4.7×10^{-2}	SD	0.0028
CRP (n: 575,531)	CRP (SD)	Cerebral WMH volume	0.01 (-0.07; 0.09)	137	MR Egger	0.0000	214.52	8.5×10^{-1}	white	0.0028
CRP (n: 575,531)	CRP (SD)	Circulating total tau	0.20 (0.17; 0.24)	143	IVW	0.0002	209.08	1.0×10^{-100}	log2	0.0028

General:

Outcome trait abbreviations: SLE, systemic lupus erythematosus; IPF, idiopathic pulmonary fibrosis, SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; T2DM, type 2 diabetes mellitus; ALT, AST, GGT, plasma concentrations of, respectively, alanine transaminase, aspartate transaminase, γ-glutamyl transferase; cerebral WMH, white matter hyperintensity, volume.

Table S13: The *cis*-multivariable Mendelian randomization results for the effects of one standard deviation higher plasma SAP value or plasma CRP concentration.

Exposure | co-variate	Exposure (unit)	Outcome trait	Point estimate (95%CI)	No variants	model	Heterogeneity p-value	Heterogeneity chi-square statistic	p-value (scientific notation)	Unit	Multiplicity threshold
SAP | CRP	SAP (SD)	Osteoarthritis (hip)	1.11 (1.04; 1.19)	30	MR Egger	0.6400	23.83	2.98×10^{-3}	OR	0.0028
CRP | SAP	CRP log(mg/L)	Osteoarthritis (hip)	1.02 (0.93; 1.11)	30	IVW	0.2612	32.33	6.46×10^{-1}	OR	0.0028
SAP | CRP	SAP (SD)	Total brain volume	-0.00 (-0.02; 0.01)	30	IVW	0.8214	21.09	6.38×10^{-1}	SD	0.0028
CRP | SAP	CRP log(mg/L)	Total brain volume	0.04 (-0.01; 0.09)	30	IVW	0.8214	21.09	1.11×10^{-1}	SD	0.0028
SAP | CRP	SAP (SD)	Circulating total tau	0.06 (0.03; 0.08)	29	IVW	0.6120	24.33	4.55×10^{-6}	log2	0.0028
CRP | SAP	CRP log(mg/L)	Circulating total tau	0.20 (0.14; 0.25)	29	IVW	0.6120	24.33	2.62×10^{-12}	log2	0.0028