Supplementary Information

A genome-wide association study of serum proteins reveals shared loci with common diseases

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Supplementary Note 1: Novelty estimates for pQTLs reported in the current study

The current study is a genome-wide analysis of ~7.5M variants imputed using the HRC reference panel in 5,368 AGES participants and measurements of 4,782 SOMAmers. We compared the pQTLs identified in the current study to previously reported studies: a) the INTERVAL-study GWAS[1] of 3,283 SOMAmers in 3,301 individuals based on 10.6 million imputed (combined 1000 Genomes Phase 3-UK10K reference panel) autosomal variants, b) our previously published[2] *cis* pQTL (300kb window up- and downstream of gene boundaries) and *cis*-to-*trans* pQTLs analysis for 4,783 SOMAmers in 3,200 AGES participants using genetic variants imputed using the 1000 Genomes v3 reference panel and c) a recent Illumina exome array analysis[3] of 54,469 variants and 4,782 SOMAmers in up to 5,343 AGES participants, d) 17 additional proteogenomic studies with a more limited protein coverage (Supplementary Data 5).

In the current study, genetic signals were defined as shared across SOMAmers if the lead variants were in strong LD (r^2>0.9). Therefore, the same LD threshold was used to define shared genetic signals across studies based on reported lead variants. However, the study comparison was also performed using a more stringent threshold (r^2>0.5). In addition, we performed a lookup of lead independent variants in the current study in the publicly available summary statistics from the INTERVAL study[1].

As shown in Supplementary Table 1 and Supplementary Fig. 4, 1,452 (36%) associations were considered novel at the primary LD threshold and 1,188 (29%) remained so at the more stringent LD threshold. The majority of proteins (1,922 or 92%) for which we find a pQTL have a previously reported pQTL, with a large proportion originating from our recent exome chip study[3], while the current study increases considerably the number of known genetic signals for serum protein levels (38% of genetic signals defined as novel at the primary LD threshold).

Finally, we considered novelty at the locus level, in addition to an evaluation based on the independent signals. Combining independent signals within 300kb of each other, we identified 772 loci associated with protein levels. Of those, 94 (12%) are novel, in the sense that they are >500kb away from lead pQTL variants reported in other studies. Of 3,079 locus-protein associations, 565 (18%) are previously unreported. If we exclude our own exome array analysis in the AGES cohort[3], we find that 17% of the loci are novel and 40% of the locus-protein associations.

Supplementary Table 1 – Comparison of independent pQTLs (association, genetic signal and protein) identified in the current study compared to previously reported proteogenomic studies. The comparison is shown at two different LD thresholds.

				Known		Addition		Novel	
LD threshold (r2)	Study compared to	Type	Total	count	%	count	%	count	%
0.9	Sun et al. 2018	assoc	4035	1304	32.3	NA	NA	2731	67.7
0.9	Sun et al. 2018	signal	2024	707	34.9	188	9.3	1129	55.8
0.9	Sun et al. 2018	protein	2091	387	18.5	686	32.8	1018	48.7
0.9	Emilsson et al. 2018	assoc	4035	1087	26.9	NA	NA	2948	73.1
0.9	Emilsson et al. 2018	signal	2024	428	21.1	55	2.7	1541	76.1
0.9	Emilsson et al. 2018	protein	2091	485	23.2	766	36.6	840	40.2
0.9	Emilsson et al. 2020	assoc	4035	1572	39.0	NA	NA	2463	61.0
0.9	Emilsson et al. 2020	signal	2024	355	17.5	30	1.5	1639	81.0
0.9	Emilsson et al. 2020	protein	2091	728	34.8	998	47.7	365	17.5
0.9	Other	assoc	4035	332	8.2	NA	NA	3703	91.8
0.9	Other	signal	2024	202	10.0	231	11.4	1591	78.6
0.9	Other	protein	2091	73	3.5	394	18.8	1624	77.7
0.9	Any	assoc	4035	2583	64.0	NA	NA	1452	36.0
0.9	Any	signal	2024	1060	52.4	204	10.1	760	37.5
0.9	Any	protein	2091	1015	48.5	907	43.4	169	8.1
0.5	Sun et al. 2018	assoc	4035	1345	33.3	NA	NA	2690	66.7
0.5	Sun et al. 2018	signal	2024	734	36.3	244	12.1	1046	51.7
0.5	Sun et al. 2018	protein	2091	405	19.4	668	31.9	1018	48.7
0.5	Emilsson et al. 2018	assoc	4035	1252	31.0	NA	NA	2783	69.0
0.5	Emilsson et al. 2018	signal	2024	522	25.8	92	4.5	1410	69.7
0.5	Emilsson et al. 2018	protein	2091	531	25.4	720	34.4	840	40.2
0.5	Emilsson et al. 2020	assoc	4035	2009	49.8	NA	NA	2026	50.2
0.5	Emilsson et al. 2020	signal	2024	636	31.4	57	2.8	1331	65.8
0.5	Emilsson et al. 2020	protein	2091	919	44.0	807	38.6	365	17.5
0.5	Other	assoc	4035	435	10.8	NA	NA	3600	89.2
0.5	Other	signal	2024	266	13.1	296	14.6	1462	72.2
0.5	Other	protein	2091	104	5.0	363	17.4	1624	77.7
0.5	Any	assoc	4035	2847	70.6	NA	NA	1188	29.4
0.5	Any	signal	2024	1233	60.9	197	9.7	594	29.3
0.5	Any	protein	2091	1160	55.5	762	36.4	169	8.1

Supplementary Note 2: Replication of pQTLs between INTERVAL and AGES cohorts

Replication of INTERVAL study pQTLs in AGES

We performed a lookup of previously reported pQTLs from the INTERVAL study[1] (n = 3,301). The comparison was based on the reported independent variants from a conditional analysis, however comparing univariate effect sizes and P-values to our GWAS results for consistency.

Replication of pQTLs from the INTERVAL study was good, with 84.6% of reported associations directionally consistent in AGES and 75.6% both directionally consistent and nominally significant (Supplementary Table 2, Supplementary Fig. 5). While the proportion of study-wide significant associations in AGES increased with a stronger reported significance in the INTERVAL study as expected, rather surprisingly the proportion of non-significant associations remained constant around 20% independent of the reported significance (Supplementary Fig. 5C). This was explained by a large proportion of pQTLs reported in the INTERVAL study that are located on chromosome 19, where a strikingly high proportion was not replicated in AGES (Supplementary Fig. 6A). A further investigation narrowed this region down to the *NLRP12* locus (chr 19, 54,319,624-54,327,869), a *trans* hotspot reported in the INTERVAL study with a total of 391 associations, whereof only 20 were nominally significant in the current study (Supplementary Fig. 4B), with the minimum observed P-value = 0.002 in AGES at this locus compared to a minimum P-value = 6.5×10^{-244} in the INTERVAL study. Given the strong observed significance in the INTERVAL study, the associations at this locus are unlikely to be false positives, however the discrepancies between the two studies at this locus may rather reflect some cohort-specific attributes, as for instance the INTERVAL study is based on plasma samples compared to serum samples in AGES and there is a large age gap between the two cohorts. More specifically, the INTERVAL cohort consists of young (mean age ~44 years), healthy blood donors of European descent and recruited in England and the proteins are measured in plasma samples, while the population-based AGES cohort consists of elderly (mean age ~76 years) Icelanders, many of whom suffer from chronic diseases and the proteins are measured in serum samples. Others have suggested that differences in observed pQTLs in this locus may be driven by sample handling and white blood cell lysis[4]. The lead variant in the INTERVAL study at this locus (rs62143197) is an intron variant in *NLRP12*, which is also an eQTL for *NLRP12* in GTEx ($P = 3.2\times10^{-15}$ for whole blood, https://gtexportal.org/home/). A lookup of this variant in UKBB associations[5] (http://geneatlas.roslin.ed.ac.uk/) revealed strong

associations with monocyte percentage (beta = -0.12, $P = 3.4 \times 10^{-155}$) and counts (beta = -0.009, $P = 1.5 \times 10^{-141}$).

When the *NLRP12* locus was excluded from the pQTL comparison, 97.6% of associations reported in the INTERVAL study were directionally consistent in the current study and 93.3% were both directionally consistent and nominally significant (Supplementary Table 2, Supplementary Fig. 5).

Replication of AGES pQTLs in the INTERVAL study

We next performed a lookup of the pQTLs identified in the current study (n = 5,368) in summary statistics from the INTERVAL study[1] (n = 3,301). The comparison was based on the lead independent variants from the conditional analysis, however comparing univariate effect sizes and P-values for consistency between the two studies and restricted to the 4,028 associations that were study-wide significant in both the joint model (from the conditional analysis) and the univariate GWAS in AGES.

Of the 2,690 associations that could be compared between the studies, we found 94.2% to be directionally consistent and 82% were both directionally consistent and at least nominally significant ($P < 0.05$) in the INTERVAL study (Supplementary Table 2). When we restricted the comparison to 645 pQTLs defined as novel in the current study (see Supplementary Note 1) and with information available in the INTERVAL study, we still found 90% to be directionally consistent and 64% to be both directionally consistent and nominally significant ($P < 0.05$).

Supplementary Table 2 – Overview of reported independent pQTLs (linear regression) in the INTERVAL study[1] with their replication status in AGES and vice versa. The INTERVAL study results are also shown excluding the *NLRP12* locus, a *trans* hotspot in the INTERVAL study. For the current AGES study, we show the results for all associations and only those defined as novel.

Discovery	Sun et al. 2018	Sun et al. 2018 (excluding the NLRP12 locus)	AGES	AGES (novel only)
Replication	AGES	AGES	Sun et al. 2018	Sun et al. 2018
Associations (n)	1905	1514	2690	645
SNPs (n)	1046	1037	1558	467
SOMAmers (n)	1359	1022	1605	534
Directionally consistent (n (%))	1611 (84.6)	1476 (97.5)	2533 (94.2)	581 (90.1)
Nominally significant (P<0.05) in replication (n (%))	1441 (75.6)	1421 (93.9)	2219 (82.5)	414 (64.2)
Directionally consistent and nominally significant (P<0.05) in replication (n (%))	1417 (74.4)	1413 (93.3)	2198 (81.7)	412 (63.9)

Supplementary Note 3: GWAS of the serum protein co-regulatory network

We regressed 54 Eigenproteins (1st and 2nd PCs) on 7.5 million variants that were assayed or imputed in all 5,368 AGES participants with protein data. Combined, the 1st and 2nd PCs capture on average 45% of the variance in each serum protein module. We assumed an additive linear model for each module's Eigenprotein. Applying the conventional P-threshold of 5.0×10^{-8} for genome-wide significance when a linkage disequilibrium (LD) $r^2<0.8$ is used for independent variants, we find that 24 (89%) out of 27 modules are associated with at least one independent network-associated protein SNP (npSNP) (Supplementary Table 3). This is a marked increase (26%) in number of identified npSNPs compared to previous results based on 1.5 million markers in 3,219 AGES participants[2]. Applying a naive conservative Bonferroni correction for number of variants and Eigenproteins tested, 18 (67%) modules showed significant association to at least one independent npSNP at $P<1.2\times10^{-10}$. Often, certain npSNPs are associated with more than one protein module that is consistent with their relationship[2].

When the significant npSNPs listed in Supplementary Table 3 were tested against all proteins we considered associations at $P < 1\times10^{-7}$ significant, using Bonferroni correction for number of npSNPs and proteins tested. The majority of npSNPs were associated with many individual proteins in *cis* and/or *trans* (mostly *trans*), while the proteins that were affected comprised the module(s) associated with the corresponding npSNP which is in line with previous

observations[2]. For instance, four npSNPs across three chromosomal sites including a region harboring *APOE/TOMM40*, were associated with either 1st or 2nd PCs for the protein module 11 (PM11) (Supplementary Table 3). These variants were associated with 136 proteins in *cis* and/or *trans* including 96% of all proteins that constitute PM11. These results show that npSNP are linked to many co-regulated proteins and are underlying the architecture of the serum protein network.

The npSNPs associated with the module PM11, are also known variants in genome-wide association studies (GWAS) linked to Late-Onset Alzheimer´s Disease (LOAD), lipoproteins and coronary heart disease (CHD) (Supplementary Table 3). In fact, the majority of the npSNPs listed in Supplementary Table 3 have previously been linked to an array of clinical traits and complex diseases. For instance, a recent GWAS study identified a number of variants associated with immunoglobulin G N-glycosylation (IgGG)[6], but aberrant glycosylation of IgG has been linked to a number of age-related disease outcomes[7]. Here we find that the npSNPs rs35590487 and rs35592422 associated with the protein module PM20 (Supplementary Table 3), are also found to be associated with IgGG at chromosome 14[6,8]. More to the point, rs35590487 and rs35592422 were associated with 37 proteins including 56% of all proteins that comprise PM20. Other striking examples include the npSNPs associated with the 1st or 2nd PCs of the protein modules PM1, PM7, PM12-PM15 (Supplementary Table 3), but these are known GWAS risk variants for age-related macular degeneration (AMD)[9]. These and other examples[2], highlight the genetic architecture of the serum protein network and demonstrate that the protein network and the genetic risk of diseases is intimately connected.

Supplementary Table 3 – Genetic variants associated with module $E^{(q)}$s. Identification of genetic variants associated (linear regression) with different modules $E^{(q)}$s (q is the annotation for a specific module). Associations at the conventional genome-wide significant $P<5.0\times10^{-8}$ or naïve Bonferroni corrected $P<1.2\times10^{-10}$ are reported. N/A, not applicable. GWAS, phenotypes associated with the corresponding npSNP at $P<5.0\times10^{-8}$ as reported in the PhenoScanner and/or the GWAS catalogue.

Module	Cluster	1st $E^{(q)}$ npSNP	2nd $E^{(q)}$ npSNP	npSNP chr.	P-value npSNP	N proteins affected	Known GWAS**	*Cis* expression QTL (tissue)*
PM1	I	rs537179722		6	6.9E-12	36	RA, AMD, LC	SKIV2L (many)
			rs887829	2	7.9E-43	14	Bilirubin	UGT1A3 (liver)
PM2	II	rs704		17	2.4E-10	846	OPG	TMEM199 (many)
		rs12439785		15	3.2E-09	7	Myopia	None
			rs704	17	1.8E-12	846	OPG	TMEM199 (many)
PM3	II	rs11574452		4	4.5E-16	289	Albumin	PF4 (fibroblasts)
			rs115008613	1	9.9E-09	None	None	None
			rs73225360	X	4.2E-08	None	None	None
PM4	II	rs11574452		4	6.7E-10	289	Albumin	PF4 (fibroblasts)
			rs10761741	10	4.2E-08	19	MPV, TG	NRBF2 (fibroblasts)
			rs704	17	1.6E-37	846	OPG	TMEM199 (many)
PM5	II	rs2731674		5	1.5E-09	115	Height	F12 (liver)
			rs2345872	2	4.2E-08	8	None	FMNL2 (fibroblasts)
			rs75931041	11	2.0E-08	None	None	None
PM6	II	rs73088258		7	3.8E-08	6	None	None
PM7	II	rs241779		17	1E-302	729	AMD	TMEM199 (many)
			rs241775	17	1E-302	728	AMD	TMEM199 (many)
PM8	II		rs704	17	2.6E-19	846	OPG	TMEM199 (many)
PM9	II	rs1178713		3	4.1E-08	14	None	None
PM10	II	rs704		17	3.1E-72	846	OPG	TMEM199 (many)
			rs704	17	7.9E-143	846	OPG	TMEM199 (many)
			rs11574452	4	1.9E-11	289	Albumin	PF4 (fibroblasts)
			rs597808	12	1.1E-08	15	CRC, HT-H, SLE	ALDH2 (esophagus)
PM11	III	rs483082		19	4.8E-160	59	LOAD, TG	APOE (skin)
		rs1355537		3	3.1E-15	41	None	BCHE (nerve)
			rs429358	19	3.0E-231	63	LOAD, LDL, CHD	TOMM40 (brain)
			rs1260326	2	1.4E-09	26	TG, CRP, CHOL	NRBP1 (many)
PM12	III		rs704	17	1.9E-16	846	OPG	TMEM199 (many)
			rs3117116	6	9.9E-12	25	RA, MS	HLA-DRB5 (many)
			rs528298	1	5.9-09	198	AMD	CFHR1/3 (many)
PM13	III	rs528298		1	2.2E-14	198	AMD	CFHR1/3 (many)
		rs1042663		6	4.5E-13	152	RA, AMD, NV, MPV	SKIV2L (many)
		rs171360		17	7.8E-10	526	None	TMEM97 (thyroid)
		rs74480769		5	3.6E-08	111	None	C7 (many)
			rs704	17	2.2E-24	846	OPG	TMEM199 (many)
			rs74480769	5	1.8E-10	111	None	C7 (many)
			rs528298	1	5.1E-10	198	AMD	CFHR1/3 (many)

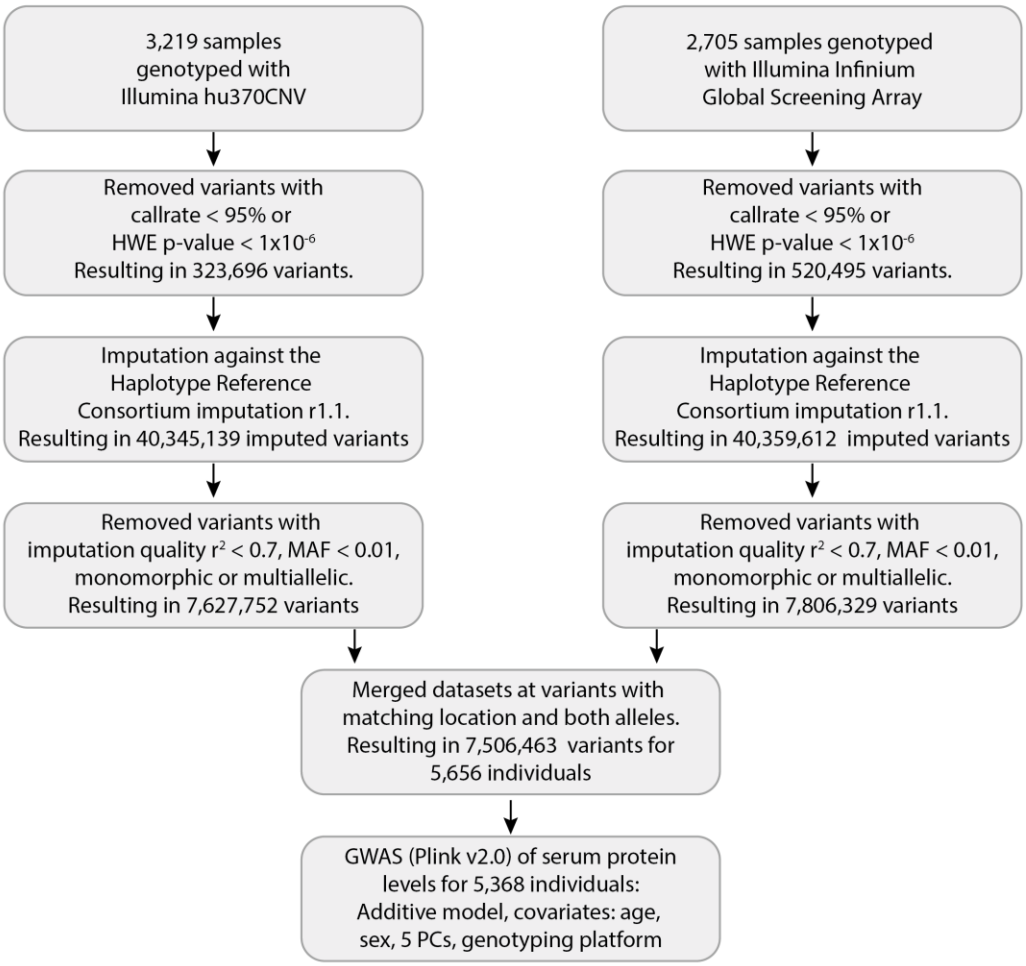
			rs115009784	6	7.9E-10	53	AMD, RA	DXO (many)
			rs11574452	4	2.9E-09	289	Albumin	PF4 (fibroblasts)
PM14	III	rs74480769		5	4.1E-11	111	None	C7 (many)
		rs1042663		6	1.2E-10	152	RA, AMD, NV, MPV	SKIV2L (many)
		rs528298		1	1.1E-09	198	AMD	CFHR1/3 (many)
		rs12067507		1	2.7E-08	56	None	None
PM15	III	rs1042663		6	2.3E-17	152	RA, AMD, NV, MPV	SKIV2L (many)
		rs528298		1	2.7E-17	198	AMD	CFHR1/3 (many)
		rs74480769		5	2.4E-14	111	None	C7 (many)
		rs171360		17	1.1E-08	526	None	TMEM97 (thyroid)
			rs115008613	1	3.7E-08	None	None	None
PM16	IV		rs11574452	4	1.9E-09	289	Albumin	PF4 (fibroblasts)
			rs61759306	1	3.9E-08	None	RBC, MCHC	SMIM1 (blood)
PM17	IV	None	None	N/A	N/A	N/A	N/A	N/A
PM18	IV	rs35120348		12	3.7E-09	5	None	METTL21B (blood)
PM19	IV	None	None	N/A	N/A	N/A	N/A	N/A
PM20	V	rs35590487		14	6.7E-18	35	IgGG	TMEM121 (many)
		rs111648045		2	3.7E-08	6 (complex)	None	None
			rs35592422	14	1.7E-25	36	IgGG	TMEM121 (many)
			rs2855812	6	6.0E-12	10	T1D, Asthma, RA	MICB (many)
			rs55800253	11	2.8E-08	None	None	None
PM21	V		rs9268833	6	4.0E-09	13	RA, Asthma	HLA (many)
PM22	V		rs3756074	4	9.2E-09	285	Albumin	PF4 (fibroblasts)
PM23	V	rs77869924		16	2.8E-08	3	None	None
			rs77625270	19	3.4E-23	1	None	TIMM44 (blood)
			rs9411378	9	4.5E-09	65	LDL, MI, VTE	ABO (many)
			rs16850360	4	4.0E-08	244	CAC	PF4 (fibroblasts)
PM24	V		rs1250258	2	1.1E-57	7	CHD, Endometriosis	ATIC (blood)
			rs5985	6	5.7E-11	3	ESC	None
			rs353634	11	7.8E-09	1	Hair colour	CD44 (artery)
PM25	V	rs185289117		14	3.0E-85	42	None	None
		rs150787591		2	7.4E-09	None	None	None
		rs4016738		3	3.2E-08	2	MC	WDR48 (blood)
			rs80324969	14	2.5E-25	38	None	CRIP2 (heart)
			rs3134998	6	2.7E-09	11	RA, Asthma	HLA (many)
PM26	V	rs76833488		15	5.7E-09	15	None	None
			rs11574452	4	1.7E-13	289	Albumin	PF4 (fibroblasts)
			rs4131289	5	2.1E-09	1	APTT, CKD	RGS14 (many)
PM27	V	None	None		N/A		N/A	N/A

*An example of *cis* expression QTL from the GTEx database.

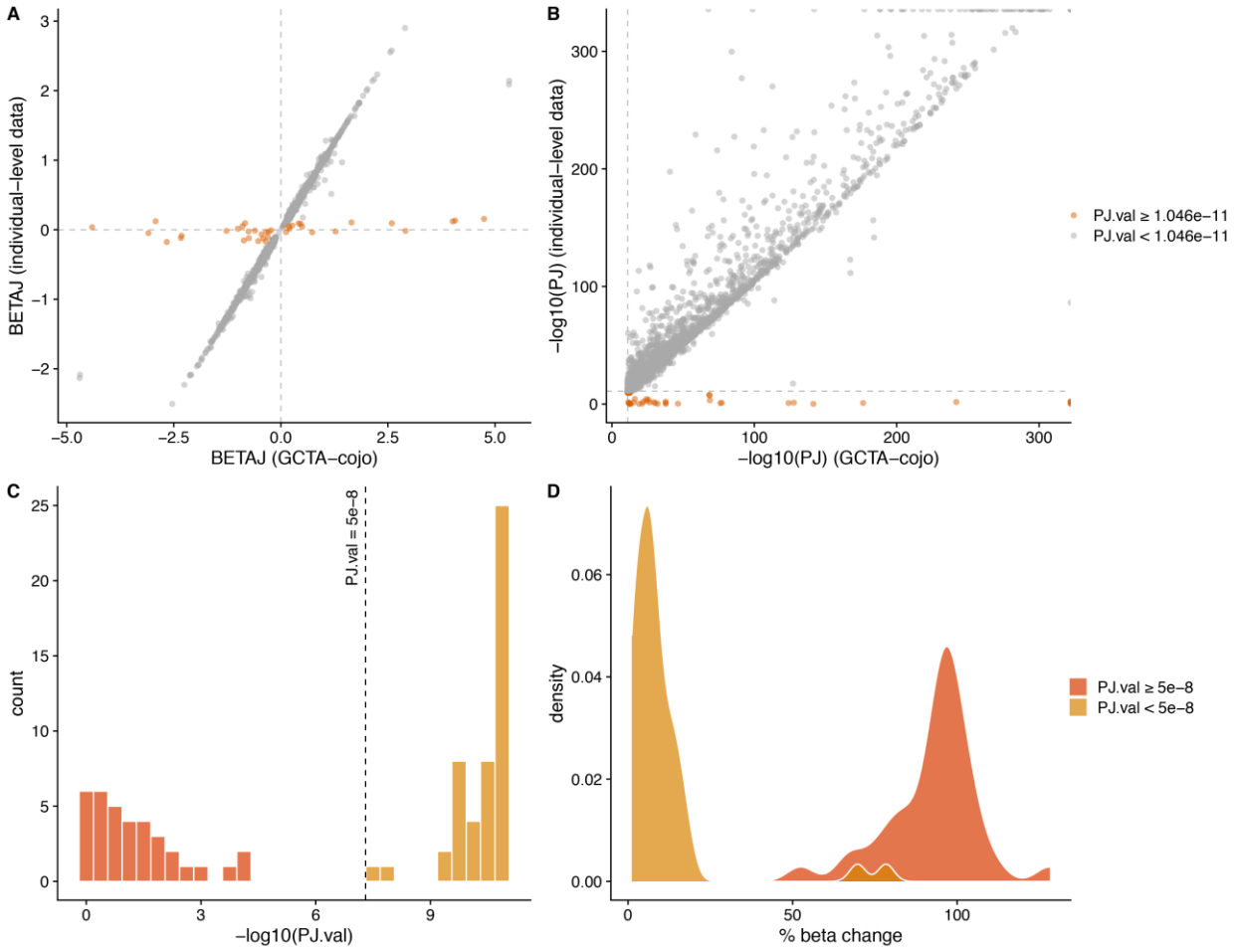
**For a qualified proxy the correlation between npSNP and corresponding lead GWAS SNP was $r^2 \geq 0.8$. Abbreviations: RA, rheumatoid arthritis; AMD, age-related macular degeneration; LC, lymphocyte count; OPG, Osteoprotegerin levels; MPV, mean platelet volume; TG, triglyceride; CRC, colorectal cancer; HT-H, hypothyroidism; SLE, systemic lupus erythrematosus; LOAD, late-onset Alzheimer´s disease; CRP, C-reactive protein;

CHOL, total cholesterol; MS, multiple sclerosis; WM, brain white matter; RBC, red blood count; MCHC, mean corpuscular hemoglobin concentration; IgGG, IgG glycosylation; T1D, type 1 diabetes; VTE, venous thromboembolism; CAC, coronary artery calcium; CHD, coronary heart disease; ESC, end-stage coagulation; MC, monocyte count; APTT, activated partial thromboplastin time ; CKD, chronic kidney disea

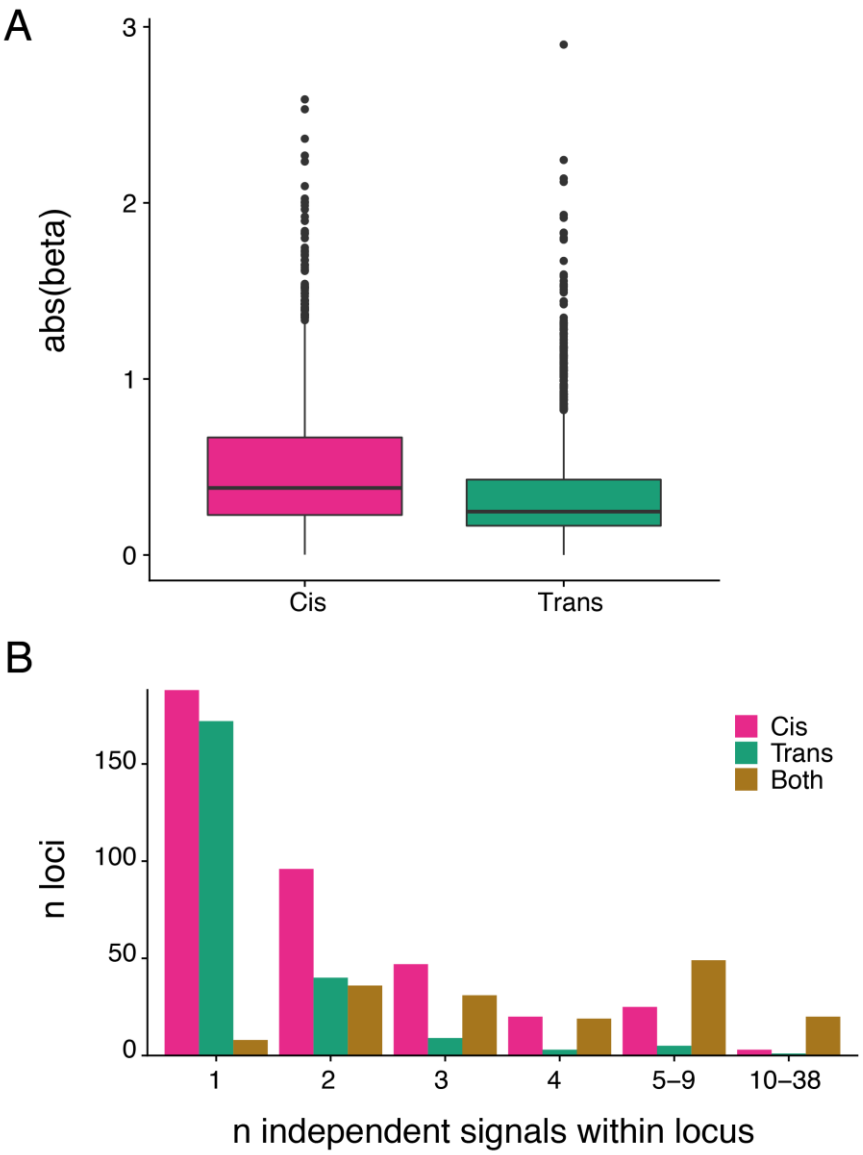
Supplementary Figures



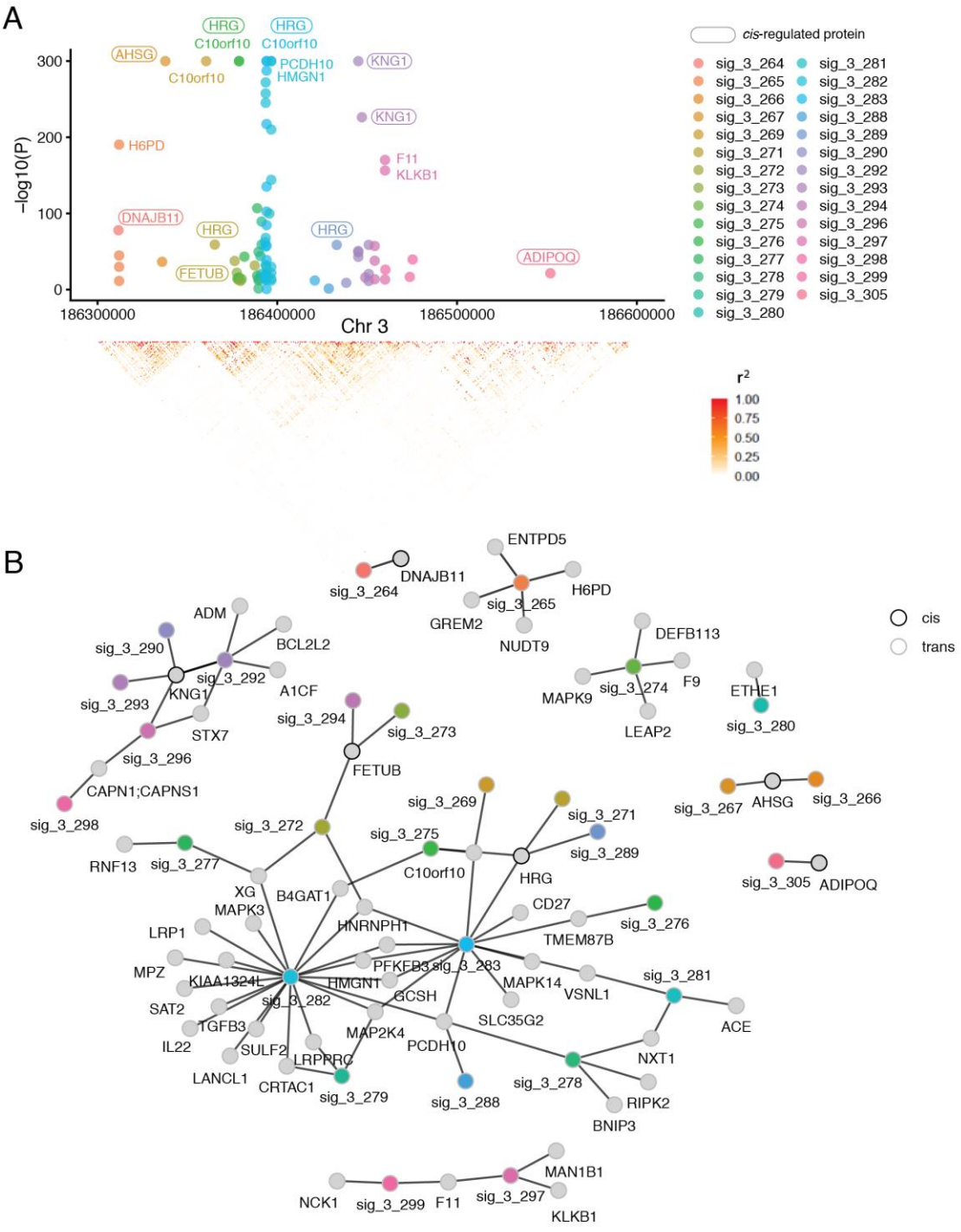
Supplementary Fig. 1 A flowchart illustrating the preprocessing steps of AGES-Reykjavik genotype data undertaken before the GWAS of serum protein levels. In short, the AGES-Reykjavik samples were genotyped using two different platforms and the resulting genotypes filtered in a similar manner before HRC imputation. The two datasets were merged after post-imputation filtering and used for the GWAS analysis, while including genotype platform among the covariates.



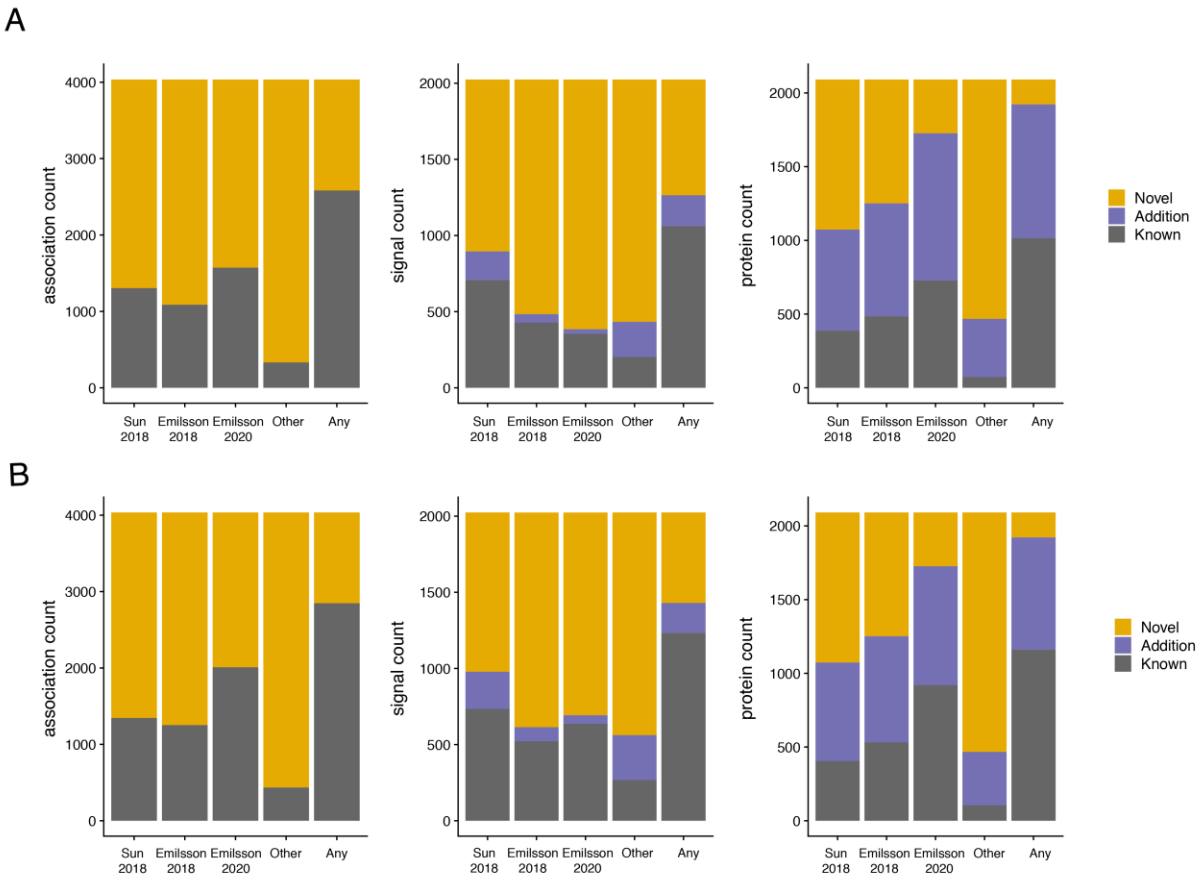
Supplementary Fig. 2 Comparison of (**A**) beta values and (**B**) –log10(P-values) for joint models of independent SNP-SOMAmer associations obtained by a conditional and joint analysis with GCTA-COJO (x-axis) and a validation analysis (linear regression) using individual level data in AGES (y-axis), colored by study-wide significance in the validation analysis. Of 4,374 SNP-SOMAmer associations, 84 (2%) did not reach study-wide significance in the validation analysis and were thus excluded from the final results. (**C**) The distribution of –log10(P-values) for the 84 SNP-SOMAmer associations not reaching study-wide significance in the validation analysis, further split those into those that reach genome-wide significance or not. (**D**) The distribution of %beta change for the 84 non-validated SNP-SOMAmer associations, stratified by reaching genome-wide significance in the validation analysis or not. The bimodal distribution suggests that a part of the non-validated associations remain borderline significant with a similar effect size (yellow) while the others are attenuated (orange) and may represent artifactual results from the GCTA-COJO analysis.



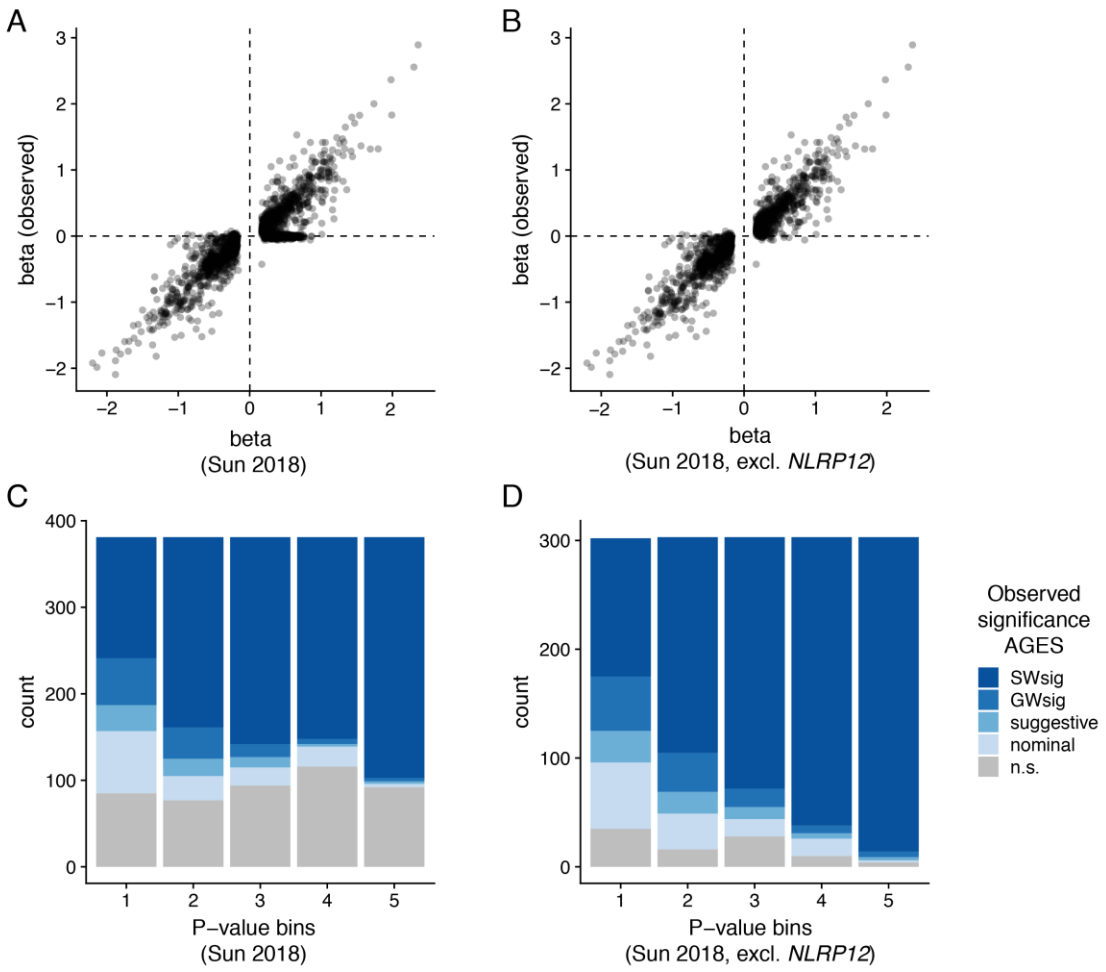
Supplementary Fig. 3 (**A**) Boxplot comparing effect sizes (absolute beta value) between *cis* (n = 1,415) and *trans* (n = 2,620) associations. Only independent associations (Supplementary Data 3) are included in the comparison and the strongest association (lowest P-value) chosen per protein if targeted by more than one SOMAmer. The median values are 0.38 (*cis*) and 0.25 (*trans*) and are significantly different (two-sided Wilcoxon's P = 1.5×10^{-6}). Boxplots indicate median value, 25th and 75th percentile, whiskers extend to smallest/largest value no further than 1.5×IQR, outliers are shown. (**B**) Barplot showing the distribution of study-wide independent signals per locus. Independent signals within 300 kb from each other were considered to share the same locus (see Methods for details).



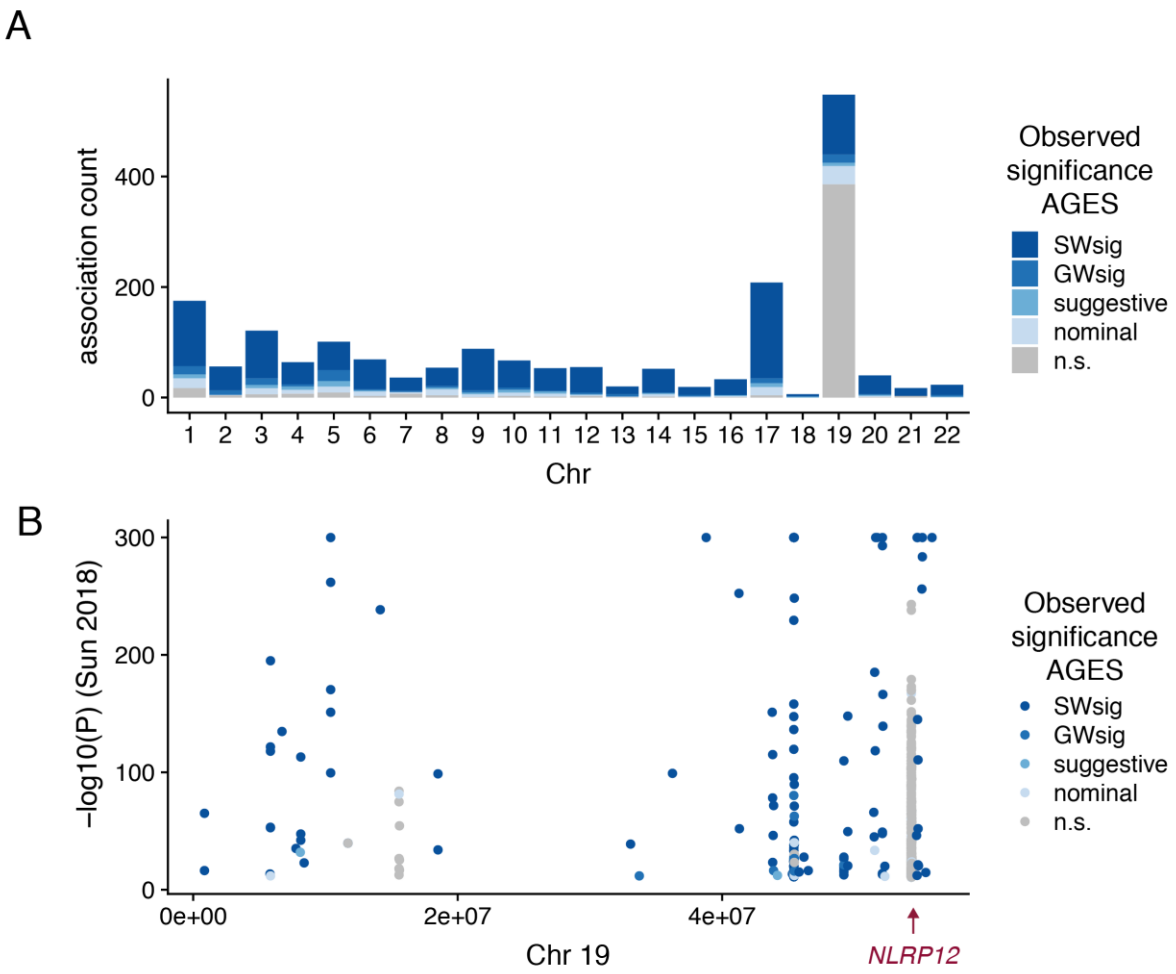
Supplementary Fig. 4 An overview of a region on chromosome 3 (186.3-186.6 Mb) where 29 independent study-wide significant signals were identified (conditional and joint analysis GCTA-COJO, n = 5,368). (**A**) Each point represents the -log10(P-value) for the associations between a given independent signal and a serum protein. The LD structure in the region (based on AGES data) is shown below. (**B**) The network demonstrates the links between independent signals in the region and serum proteins.



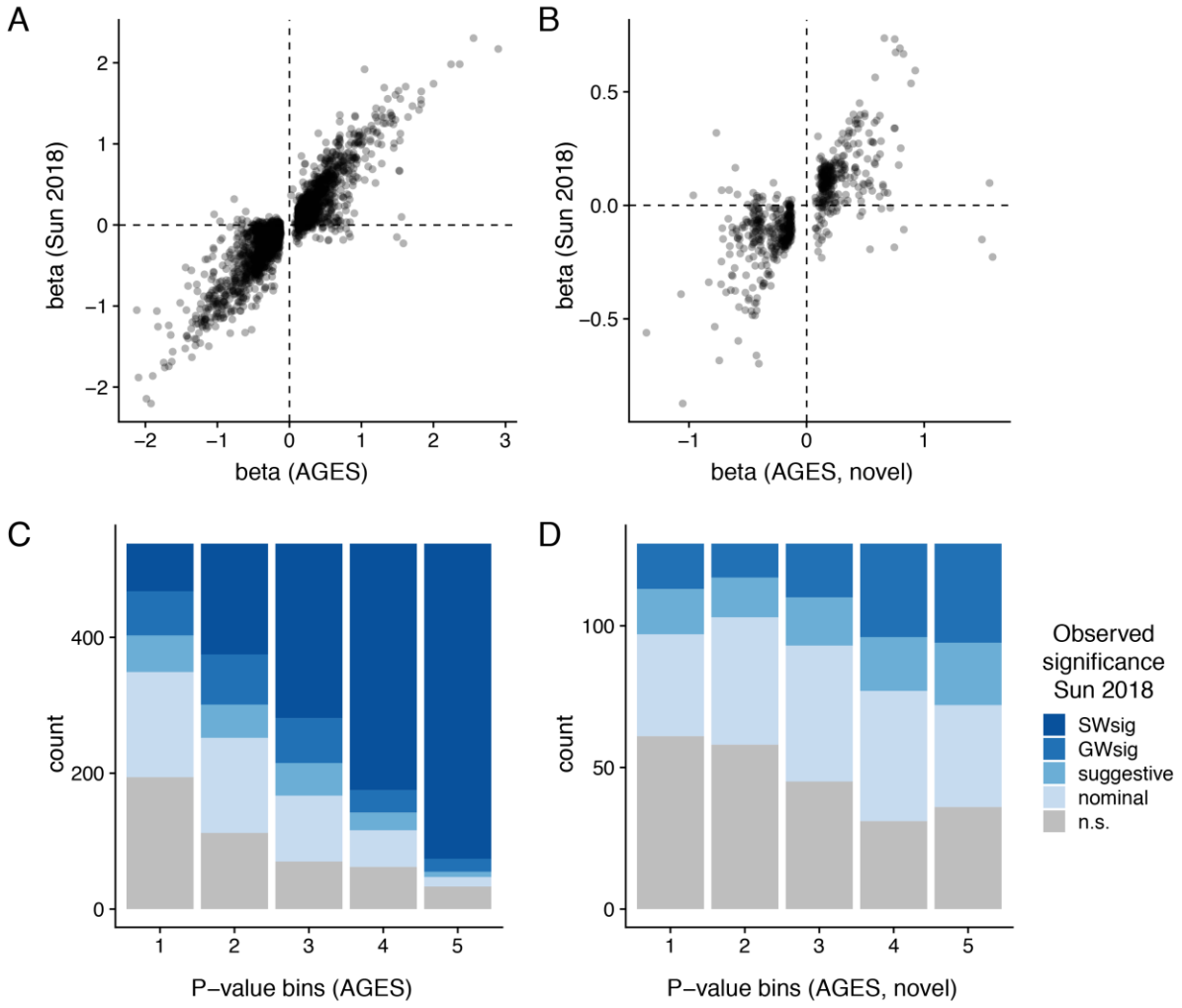
Supplementary Fig. 5 Comparison of independent study-wide significant pQTLs identified in the current study (n = 5,368) to those previously reported, using (**A**) the primary LD threshold $r^2 > 0.9$ to define shared signals, and (**B**) a more stringent LD threshold $r^2 > 0.5$ to define shared signals. The barplots show if a matching pQTL association (left panel) has been previously reported, if a genetic signal (middle panel) has been reported to associate with the same (known) or another (addition) protein, and if the same (known) or another (addition) genetic signal has previously been reported for a given protein (right panel). See Supplementary Table 1 for exact numbers. An overview of the studies used for comparison is shown in Supplementary Data 5.



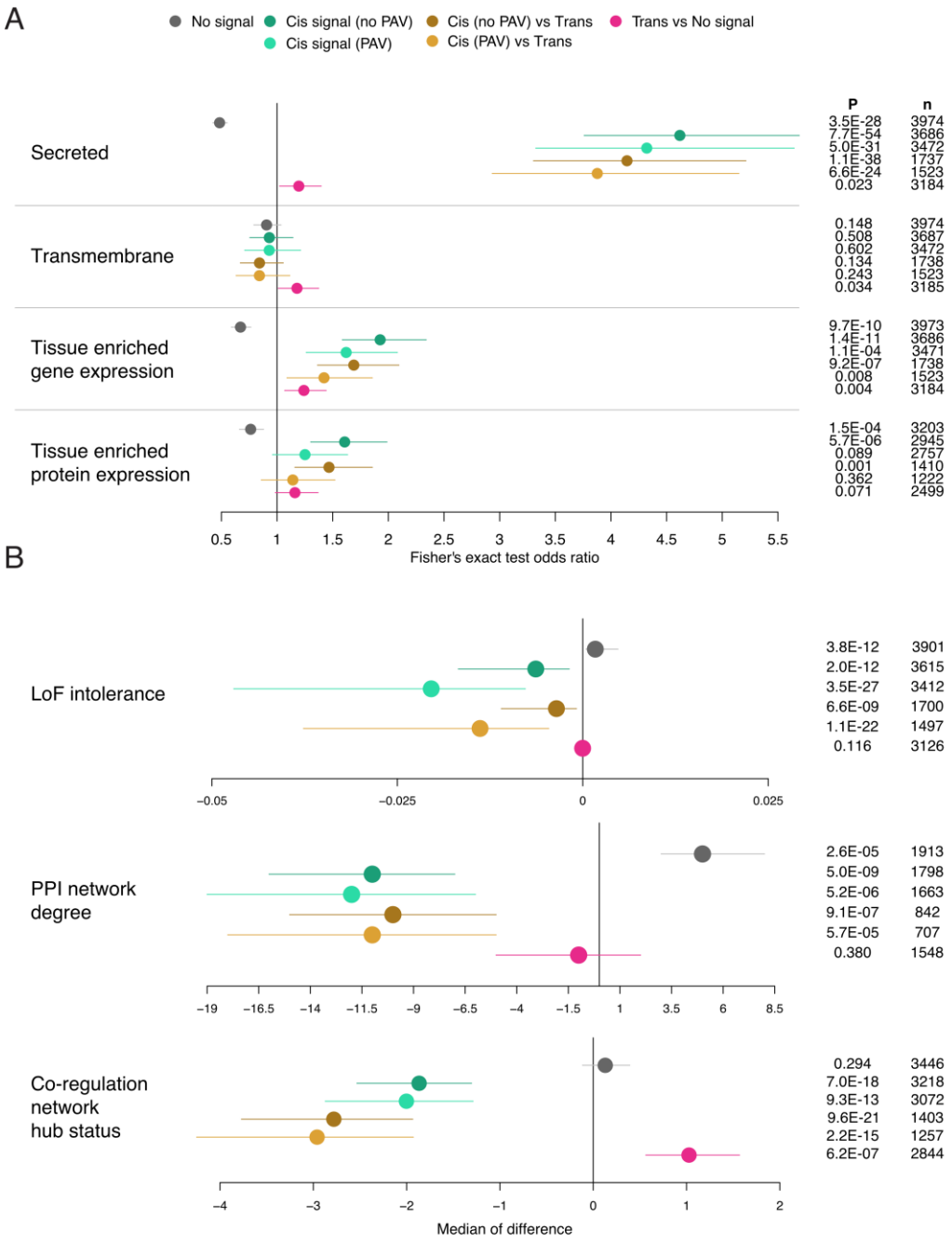
Supplementary Fig. 6 Replication of previously reported pQTLs from the INTERVAL study[1] in AGES. (**A-B**) Comparison of reported pQTL beta values for (**A**) all independent study-wide significant pQTLs reported by Sun et al.[1]. (**B**) all independent study-wide significant pQTLs reported by Sun et al.[1], but excluding the *NLRP12* locus, with matching pQTL beta values observed in the current study (linear regression, n = 5,368). (**C-D**) Number of pQTLs colored by observed significance level in the current study and shown by significance bins based on reported pQTL P-values for (**C**) all independent study-wide significant pQTLs reported by Sun et al.[1] and (**D**) all independent study-wide significant pQTLs reported by Sun et al.[1], but excluding the *NLRP12* locus, where bin 5 has the lowest (most significant) reported P-values. SWsig: study-wide significant, $P<5\times10^{-8}/4782$, GWsig: genome-wide significant, $P<5\times10^{-8}$, suggestive: $P<1\times10^{-5}$, nominal: $P<0.05$, n.s.: not significant, $P>0.05$.



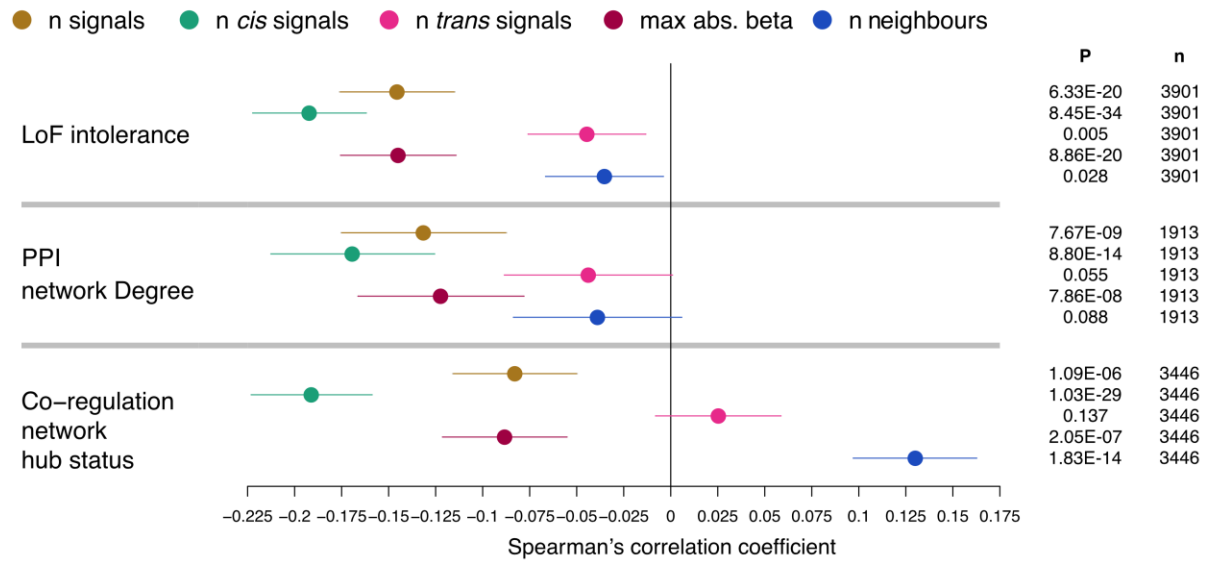
Supplementary Fig. 7 (**A**) Number of reported independent study-wide significant associations (pQTLs) by Sun et al.[1] from the INTERVAL study by chromosome, colored by observed significance level in AGES (n = 5,368). (**B**) Independent study-wide significant pQTLs reported by Sun et al.[1] on chromosome 19 colored by significance level in AGES (linear regression, n = 5,368). The *NLRP12* locus is highlighted. SWsig: study-wide significant, $P<5\times10^{-8}/4782$, GWsig: genome-wide significant, $P<5\times10^{-8}$, suggestive: $P<1\times10^{-5}$, nominal: $P<0.05$, n.s.: not significant, $P>0.05$.



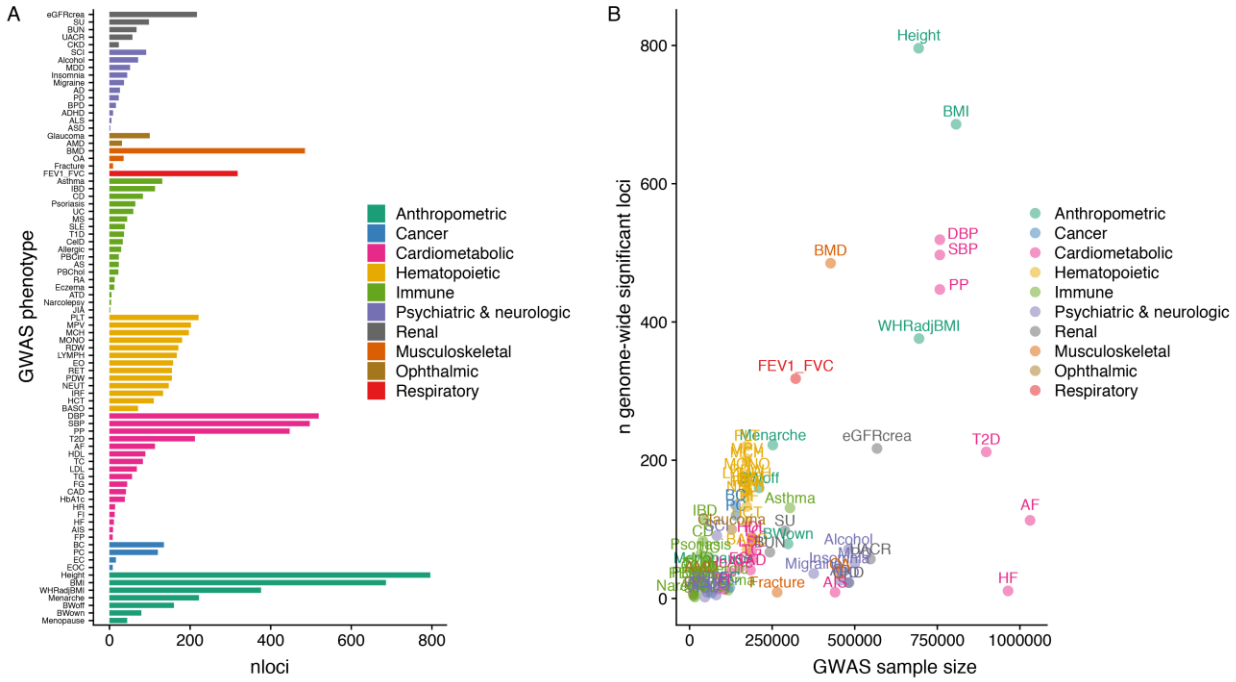
Supplementary Fig. 8 Replication of pQTLs identified in the current study (linear regression) using summary statistics from the INTERVAL study[1]. (**A**-**B**) Comparison of beta values for (**A**) all independent study-wide significant pQTLs in AGES (conditional and joint analysis, GCTA-COJO) and (**B**) independent study-wide significant pQTLs defined as novel in the current study, with matching pQTL beta values from Sun et al.[1]. (**C**-**D**) Number of pQTLs binned by P-values in the current study, shown for (**C**) all independent study-wide significant pQTLs and (**D**) independent study-wide significant pQTLs defined as novel in the current study, where bin 5 has the lowest (most significant) P-values, colored by significance level in the INTERVAL study[1]. SWsig: study-wide significant, $P<5\times10^{-8}$/3,283 (number of SOMAmers in INTERVAL study[1]), GWsig: genome-wide significant, $P<5\times10^{-8}$, suggestive: $P<1\times10^{-5}$, nominal: $P<0.05$, n.s.: not significant, $P>0.05$.



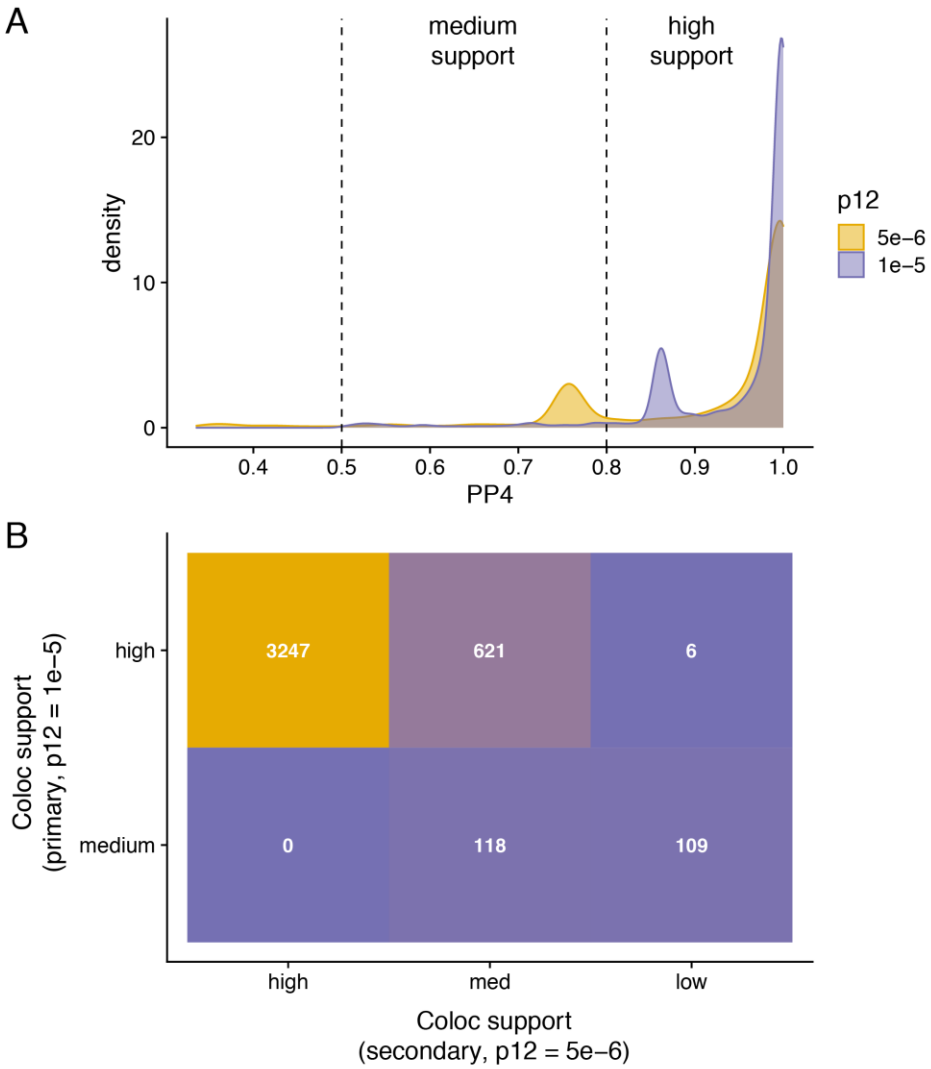
Supplementary Fig. 9 Enrichment analysis comparing characteristics between proteins classified by types of genetic association signals, where *cis*-signals are stratified by tagging a protein-altering variant (PAV) affecting the corresponding gene for the protein target or not and compared to those without any *cis*-signal. See Methods text for definitions. (**A**) Fisher's exact test (two-sided) for comparing two classifications. Odds ratio estimates are presented with 95% confidence interval. (**B**) Wilcoxon's rank sum test (two-sided) for comparing classifications with continuous traits. Estimates of the median of the difference between values from the two classes are presented with 95% confidence interval. P-values are shown to the right.



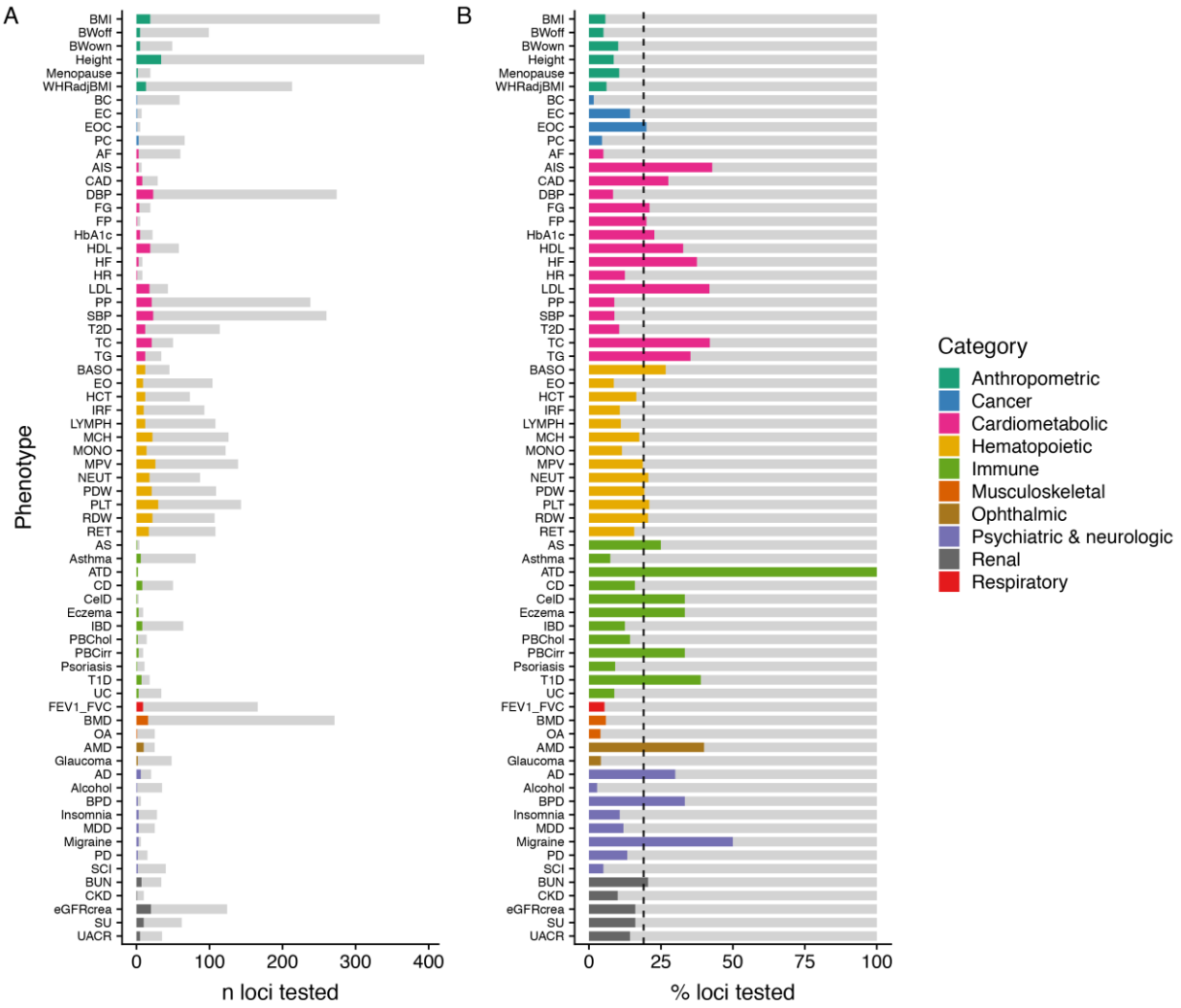
Supplementary Fig. 10 Comparing genetic association profile characteristics (number of signals in total, cis or trans, largest absolute effect size among study-wide significant independent pQTLs, and number of neighbors defined as the number of proteins that share the same genetic signal) for proteins to metrics of loss-of-function (LoF) intolerance, protein-protein interaction (PPI) network degree and co-regulation network hub status. Spearman's rank correlation coefficient estimates are presented with 95% confidence interval. P-values are calculated via an asymptotic t-distribution approximation (two-sided) and are shown to the right.



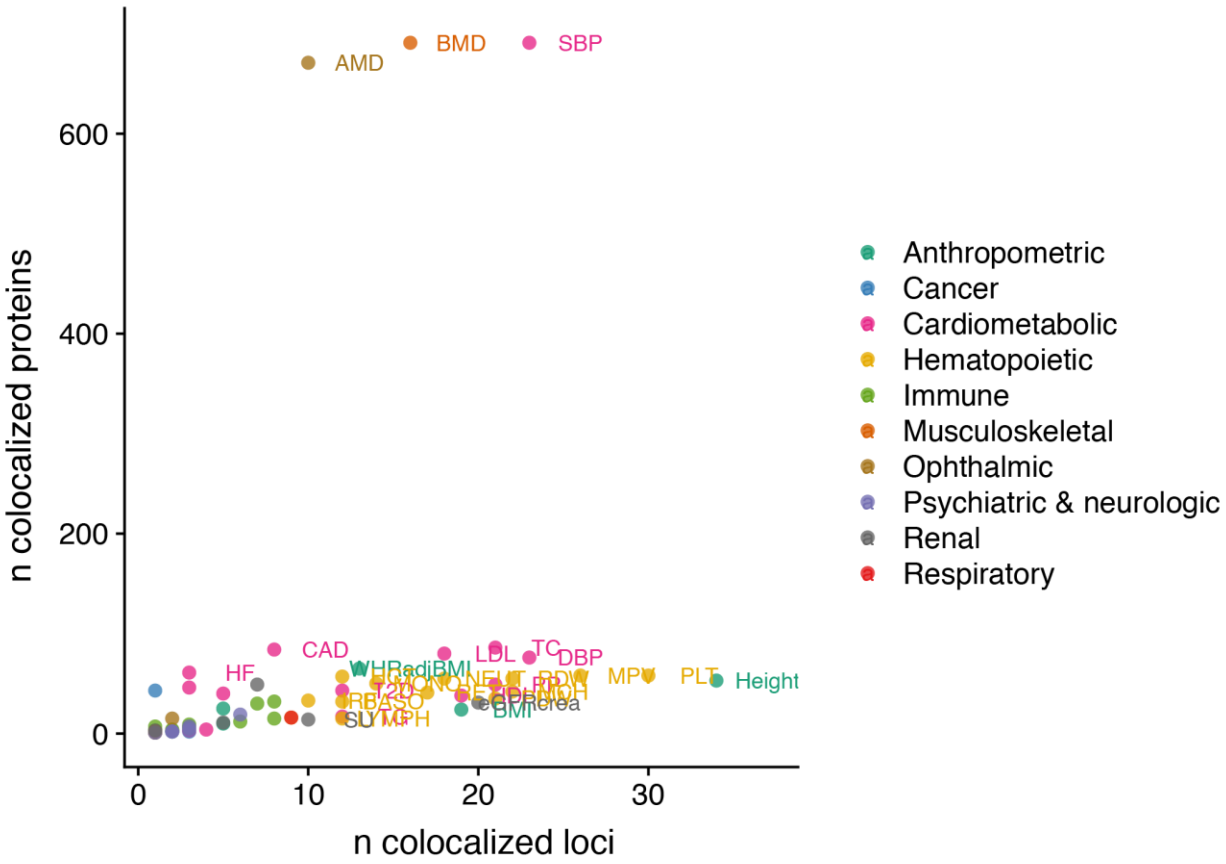
Supplementary Fig. 11 (**A**) An overview of the number of genome genome-wide significant loci (x-axis) for GWAS of 81 clinical traits and diseases (y-axis) for which summary statistics were included in the colocalization analysis with serum proteins. (**B**) An overview of the GWAS sample sizes (x-axis) and the number of genome-wide significant loci (y-axis) for the 81 clinical traits and diseases for which GWAS summary statistics were included in the colocalization analysis with serum proteins. GWAS for immune traits, in particular, have smaller sample sizes and, as a result, fewer identified loci than other trait categories.



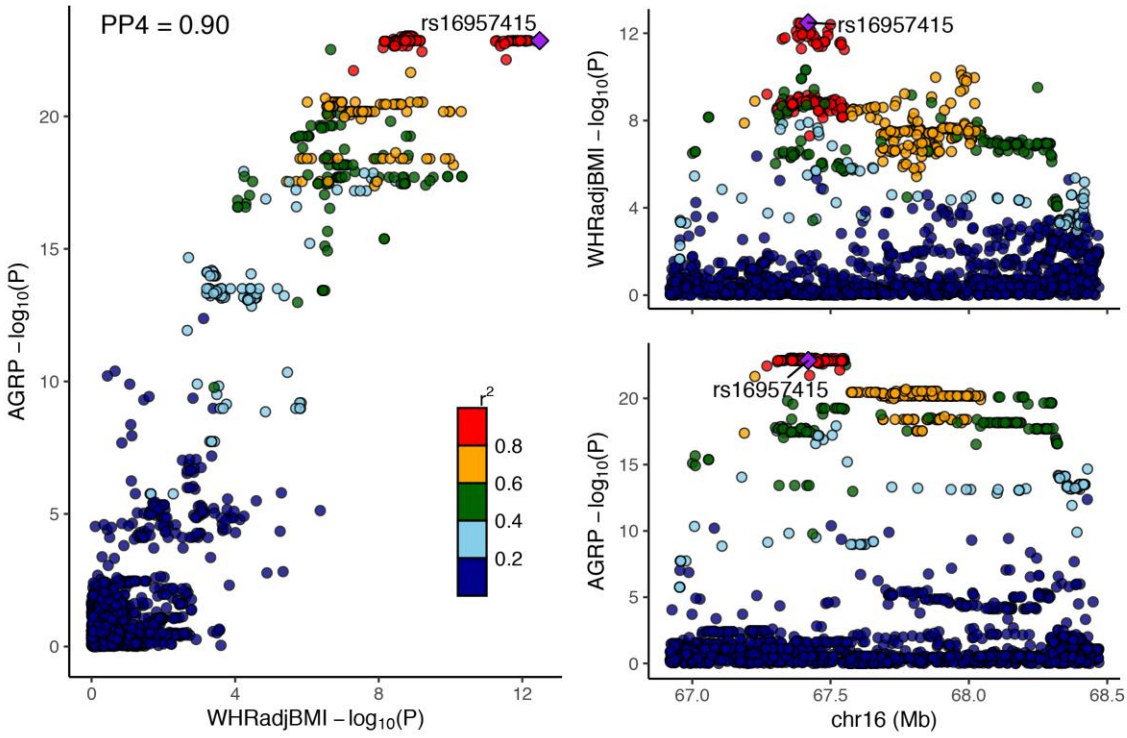
Supplementary Fig. 12 (**A**) Comparison of posterior probability values for a shared signal (PP4) obtained from coloc in the colocalization analysis for two different priors; the default coloc value of 1e-5 (primary analysis) and a more stringent value of 5e-6 (secondary analysis). The vertical dashed lines indicate the cutoffs used to define medium (PP4>0.5) and high (PP4>0.8) support for colocalization. The more stringent prior shifts some protein-phenotype pairs below the 0.8 cutoff. (**B**) The number of protein-phenotype pairs in each coloc support category using the two different priors in the primary and secondary analysis. Of the 3,874 pairs with high support in the primary analysis, 84% remain so in the secondary analysis with a more stringent prior.



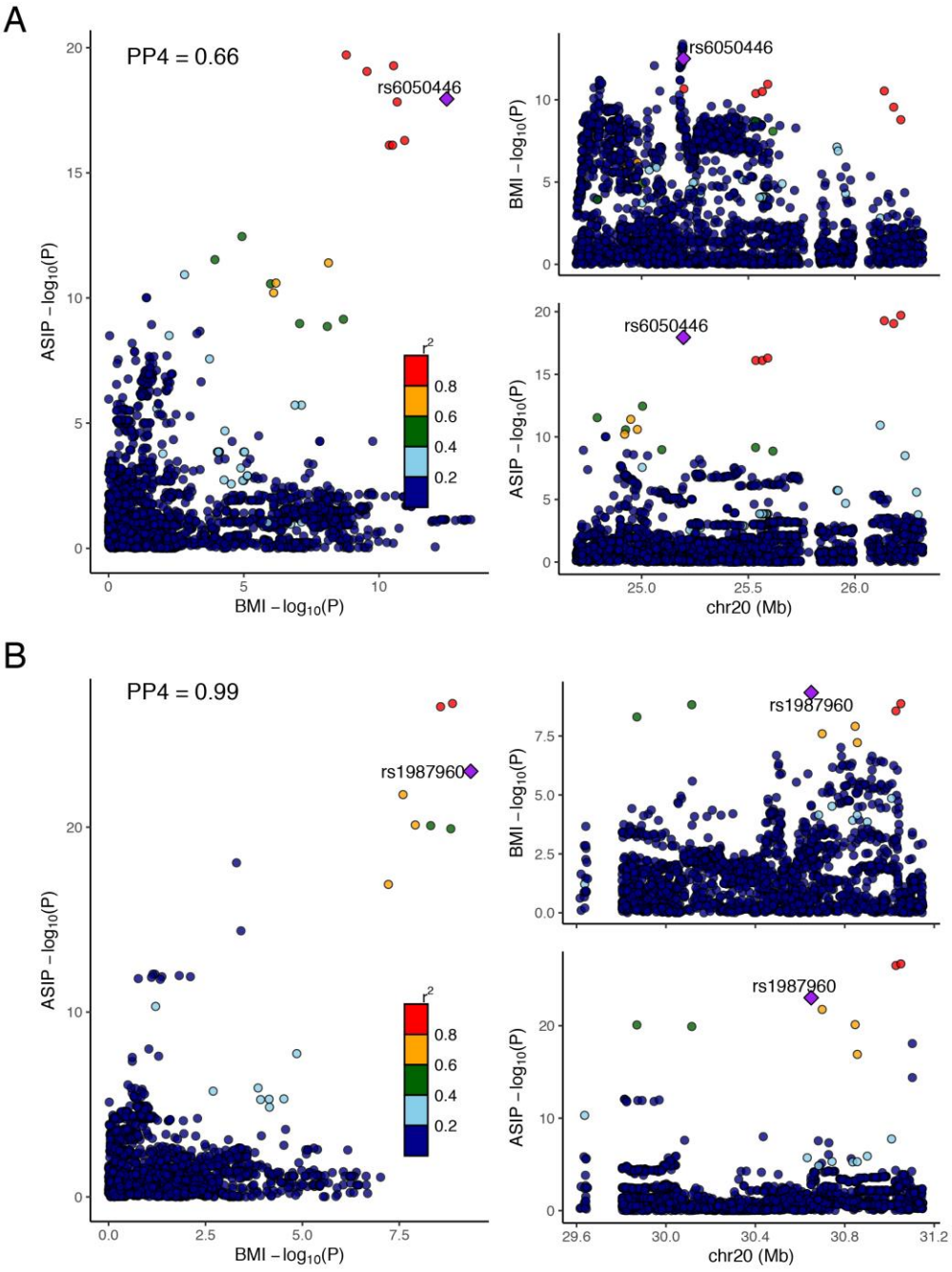
Supplementary Fig. 13 An overview of the (**A**) number and (**B**) proportion of GWAS loci that colocalize with any serum protein signal in the current study, restricted to the loci that were in the vicinity of a pQTL and thus tested. The dashed line indicates the average for the tested loci, or 19% that colocalize with at least one serum protein (whereas it is 11% when considering all GWAS loci).



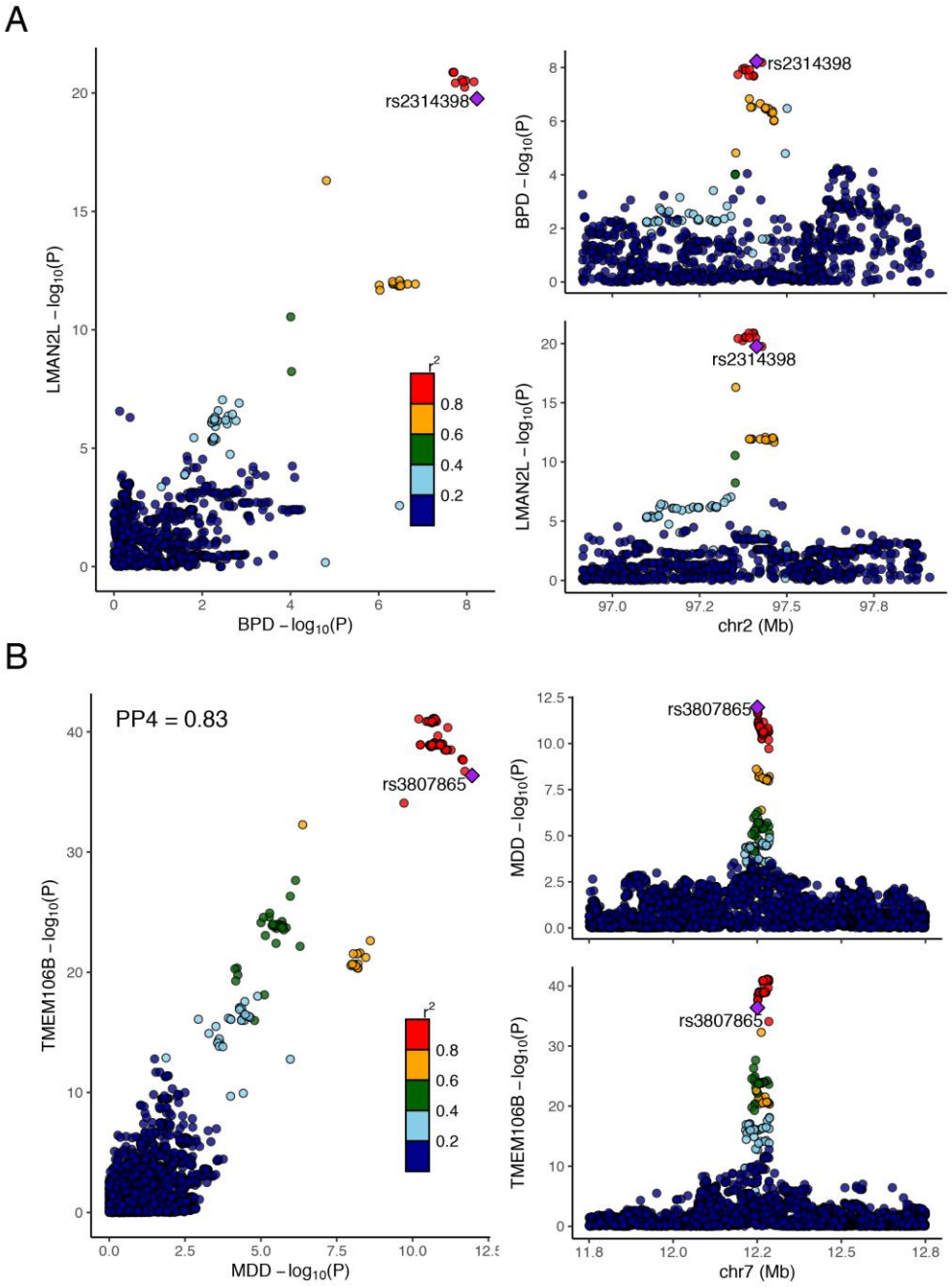
Supplementary Fig. 14 An overview of the number of colocalized proteins (y-axis) compared to the number of colocalized loci (x-axis) per trait. The three traits (AMD, BMD, SBP) at the top all colocalize with the *VTN* locus, which regulates 597 proteins.



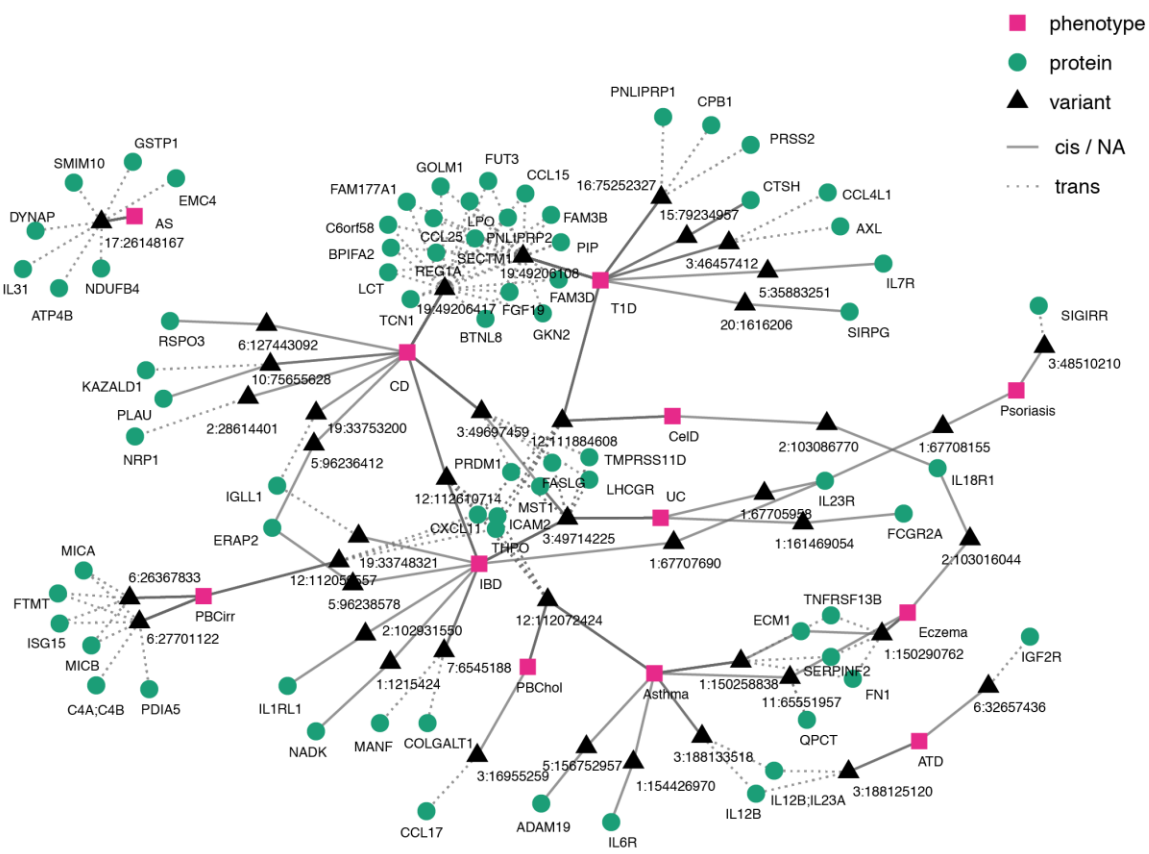
Supplementary Fig. 15 Colocalization of genetic associations (linear regression) for serum levels of the AGRP protein and waist-to-hip ratio adjusted for BMI (WHRadjBMI) on chromosome 16.



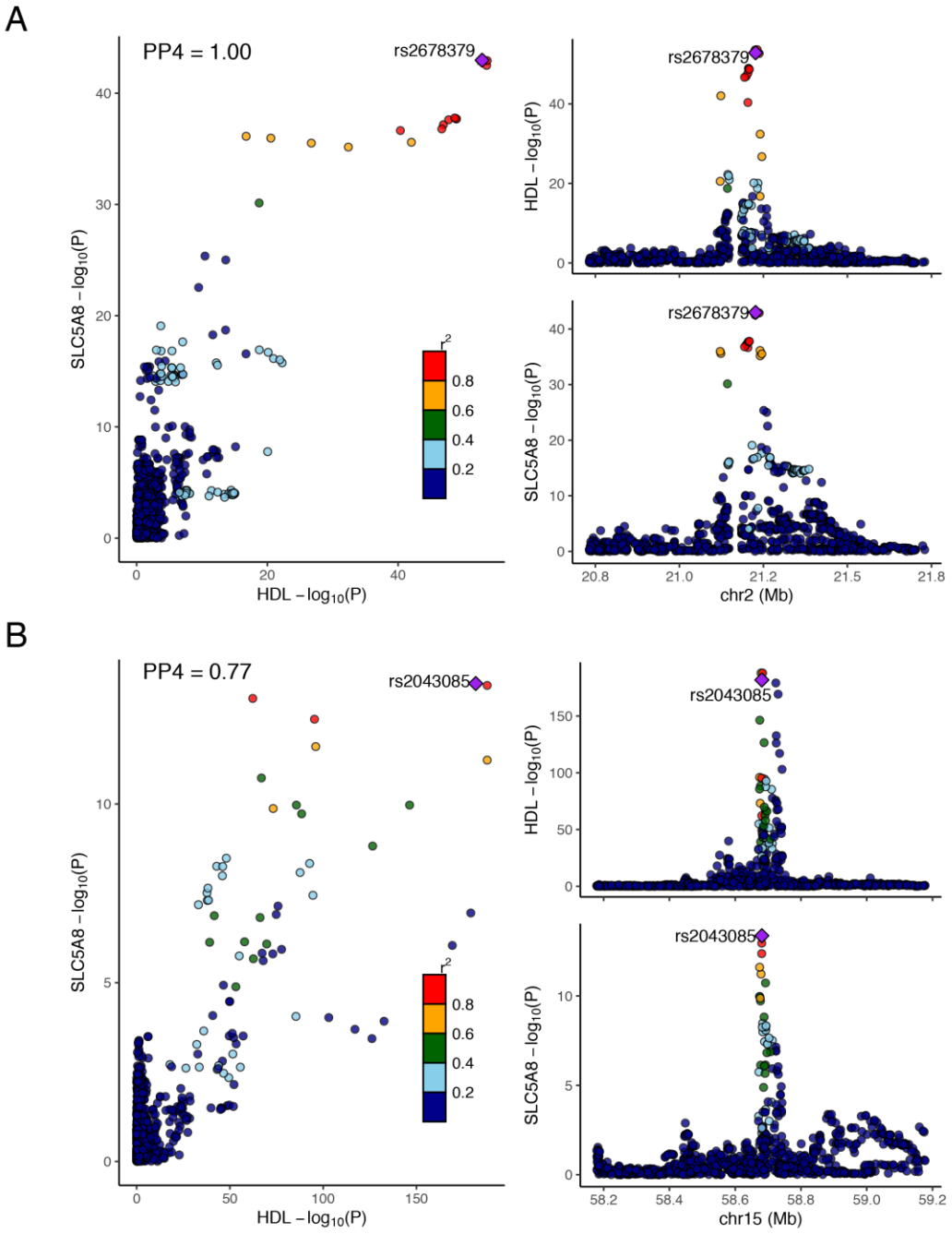
Supplementary Fig. 16 Colocalization of two genetic associations (linear regression) for serum levels of the ASIP protein and BMI on chromosome 20 at around (**A**) 25.5Mb and (**B**) 30.4Mb.



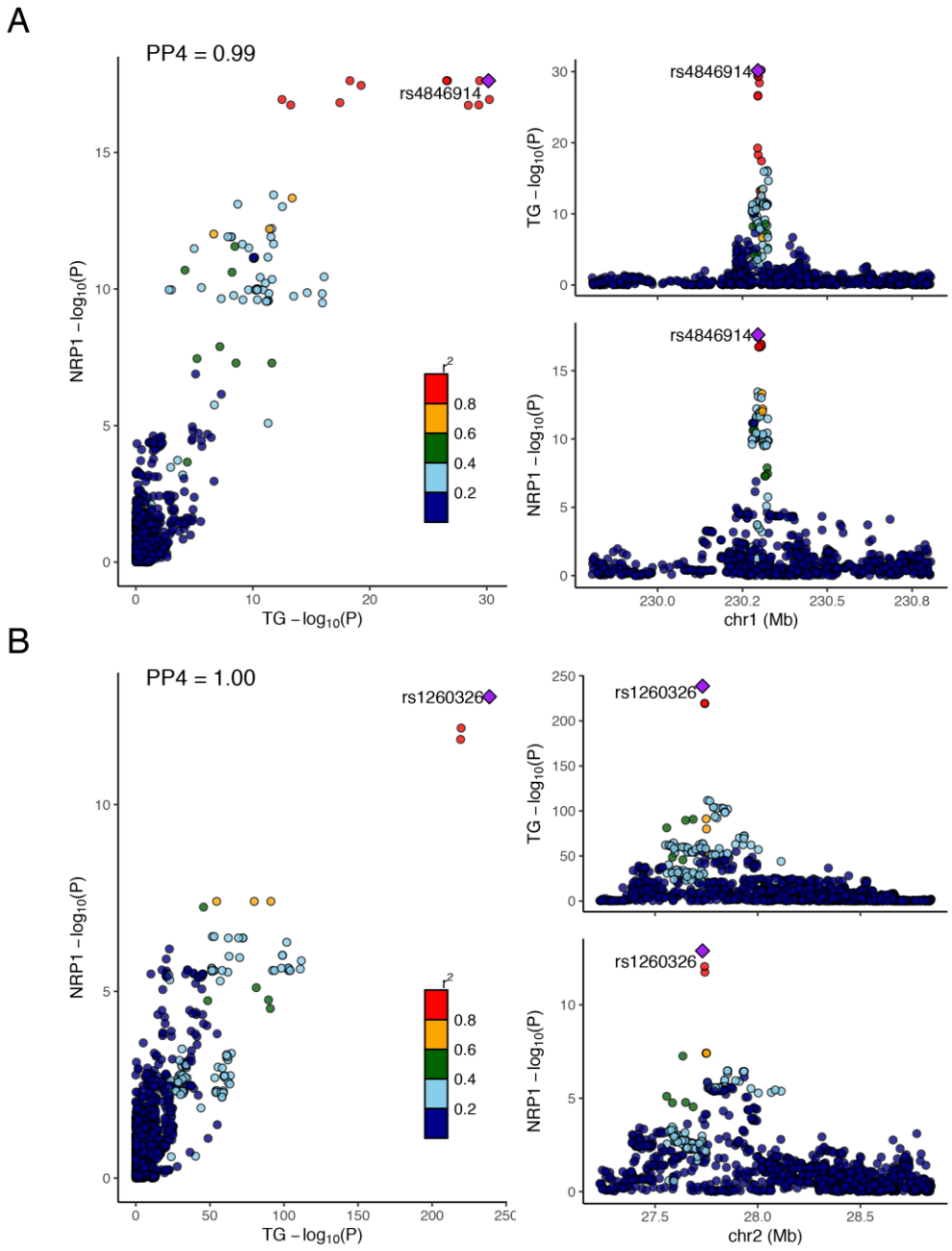
Supplementary Fig. 17 Colocalization between genetic associations (linear regression) for (**A**) serum levels of the LMAN2L protein and bipolar disorder (BPD) on chromosome 2 and (**B**) serum levels of the TMEM106B protein and major depressive disorder (MDD) on chromosome 7.



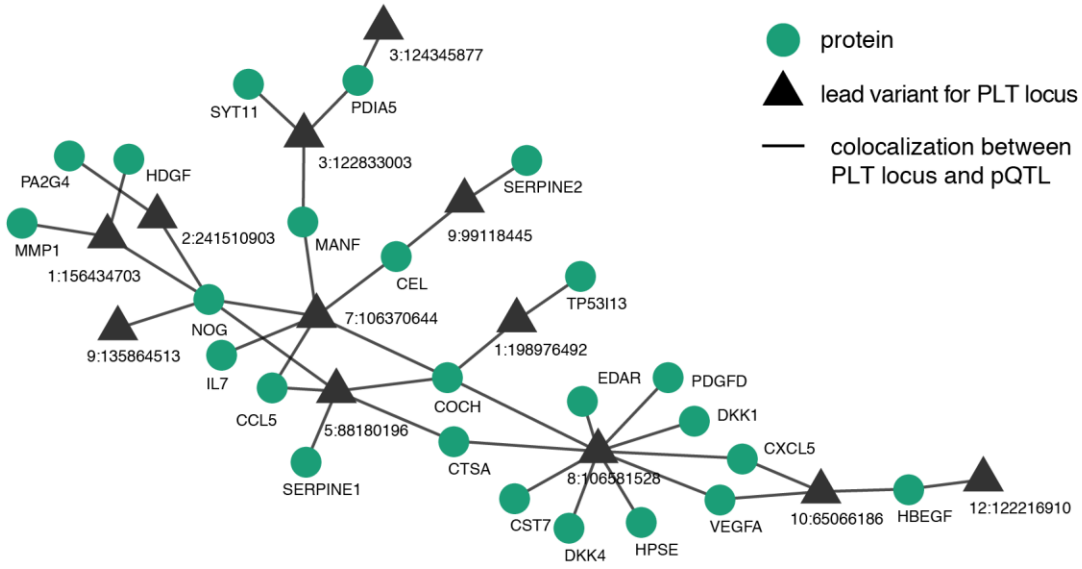
Supplementary Fig. 18 Immune disease colocalization network, illustrating how diseases (pink squares) are linked through the overlap of colocalized proteins (green circles). Diseases and proteins are linked through lead variants (black triangles) in the loci where genetic signals colocalize, where the pQTL may be in *cis* (solid line) or *trans* (dotted line).



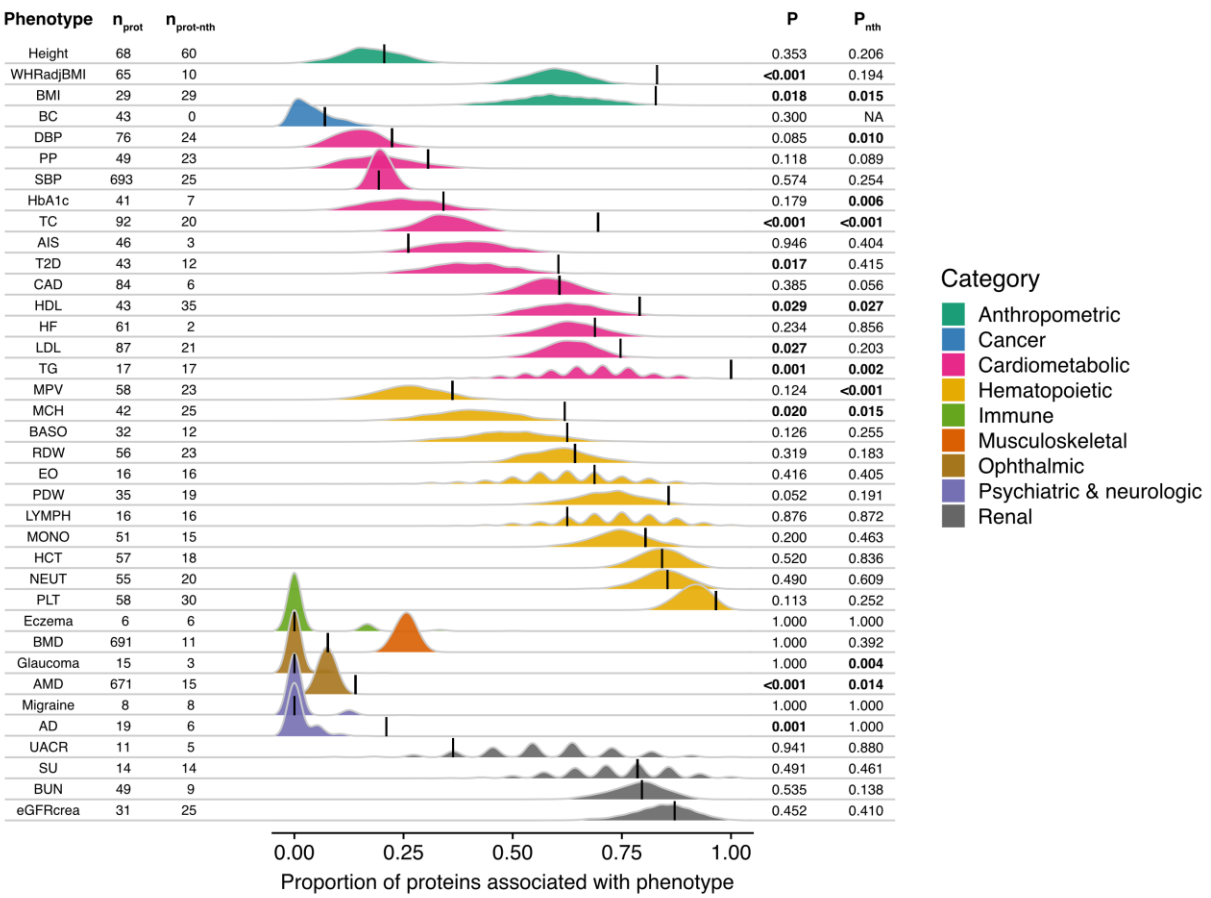
Supplementary Fig. 19 Colocalization between genetic associations (linear regression) for serum levels of the SLC58A protein and HDL cholesterol on (**A**) chromosome 2 and (**B**) chromosome 15.



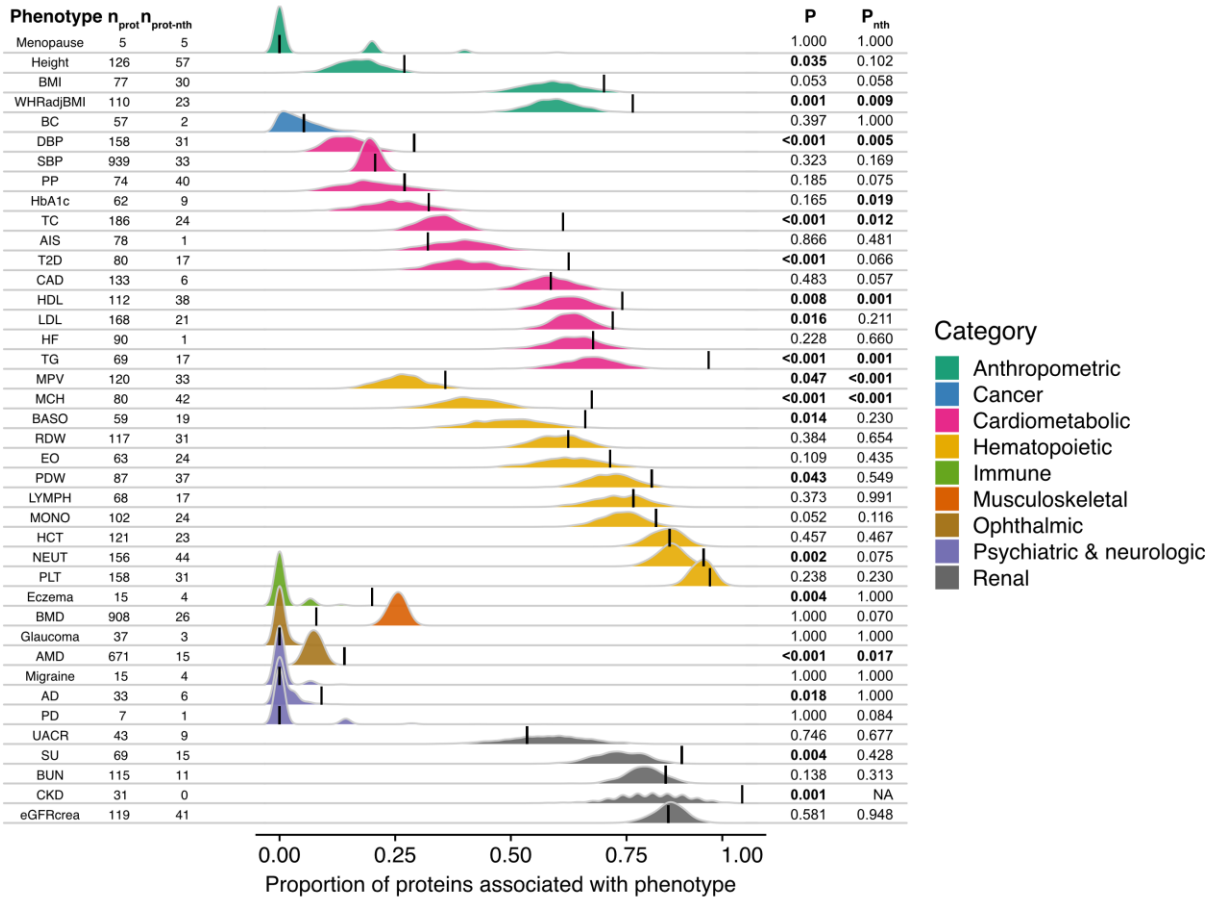
Supplementary Fig. 20 Colocalization between genetic associations (linear regression) for serum levels of the NRP1 protein and triglycerides (TG) on (**A**) chromosome 1 and (**B**) chromosome 2.



Supplementary Fig. 21 Platelet colocalization network, illustrating how many of the same proteins (green circles) colocalize with GWAS signals for platelet count (PLT) in multiple loci, represented by lead variants (black triangles). For example, pQTLs for NOG and COCH colocalize with GWAS signals for platelet counts in five and four loci, respectively.



Supplementary Fig. 22 Ridgeline plot illustrating for each GWAS phenotype the proportion of colocalized proteins including study-wide significant ($P<1.046\times10^{-11}$) pQTLs (linear regression, n = 5,368) that were significantly associated with the same trait in AGES (linear regression, FDR<0.05, n = 5,457) (black lines) compared to 1000 randomly sampled sets of proteins of the same size (density curves). The number of colocalized proteins for each trait are provided on the left-hand side, along with the number of proteins remaining after the removal of proteins originating from loci with 5 or more colocalized proteins from the analysis, annotated as “no trans-hotspots” (nth). Empirical P-values for significant enrichment of protein-phenotype associations are provided to the right. Empirical P-values < 0.05 are highlighted in bold.



Supplementary Fig. 23 Ridgeline plot illustrating for each GWAS phenotype the proportion of colocalized proteins including all genome-wide significant ($P<5\times10^{-8}$) pQTLs (linear regression, n = 5,368) that were significantly associated with the same trait in AGES (linear regression, FDR<0.05, n = 5,457) (black lines) compared to 1000 randomly sampled sets of proteins of the same size (density curves). The number of colocalized proteins for each trait are provided on the left-hand side, along with the number of proteins remaining after the removal of proteins originating from loci with 5 or more colocalized proteins from the analysis, annotated as “no trans-hotspots” (nth). Empirical P-values for significant enrichment of protein-phenotype associations are provided to the right. Empirical P-values < 0.05 are highlighted in bold.

Supplementary References

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