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

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The mechanisms responsible for neuronal death causing cognitive loss in Alzheimer's disease (AD) and many other dementias are not known. Serum amyloid P component (SAP) is a constitutive plasma protein, which is cytotoxic for cerebral neurones and also promotes formation and persistence of cerebral A β amyloid and neurofibrillary tangles. Circulating SAP, which is produced exclusively by the liver, is normally almost completely excluded from the brain. Conditions increasing brain exposure to SAP increase dementia risk, consistent with a causative role in neurodegeneration. Furthermore, neocortex content of SAP is strongly and independently associated with dementia at death. Here, seeking genomic evidence for a causal link of SAP with neurodegeneration, we meta-analysed three genome-wide association studies of 44 288 participants, then conducted *cis*-Mendelian randomization assessment of associations with neurodegenerative diseases. Higher genetically instrumented plasma SAP concentrations were associated with AD (odds ratio 1.07, 95% confidence interval (CI) 1.02; 1.11, $p = 1.8 \times 10^{-3}$), Lewy body dementia (odds ratio 1.37, 95%CI 1.19; 1.59, $p = 1.5 \times 10^{-5}$) and plasma tau concentration (0.06 log₂(ng l⁻¹) 95%CI 0.03; 0.08, $p = 4.55 \times 10^{-6}$). These genetic findings are consistent with neuropathogenicity of SAP. Depletion of SAP from the blood and the brain, by the safe, well tolerated, experimental drug miridesap may thus be neuroprotective.

1. Introduction

The direct causes and mechanisms of neuronal cell death responsible for the cognitive loss in Alzheimer's disease (AD) and many other dementias are not known. Serum amyloid P component (SAP) is an almost invariant, constitutive, normal plasma glycoprotein produced exclusively in the liver. It circulates at a mean (SD) concentration of about 24 (8) mg l⁻¹ in women and 32 (7) mg l⁻¹ in men [1] but it is normally rigorously excluded from the central nervous system. Cerebrospinal fluid (CSF) concentrations of SAP are one thousand-fold lower

than the plasma concentration [2,3], presumably reflecting relative impermeability of the blood–brain barrier (BBB). There is also evidence for an active transport mechanism exporting SAP from the CSF back into the blood [4]. SAP is named for its universal presence in all human amyloid deposits, which reflects the avid but reversible calcium-dependent binding of SAP to all types of amyloid fibrils regardless of their protein composition [5,6]. Thus, although CSF and brain content of SAP are normally extremely low, SAP is nonetheless always present in the intracerebral A β amyloid plaques, cerebrovascular A β amyloid deposits and the majority of neurofibrillary tau tangles in AD. The binding of SAP stabilizes amyloid fibrils [7] and promotes their formation [8,9], thereby contributing to amyloid deposition and persistence [10]. Furthermore, accumulation of SAP on intracerebral amyloid plaques, cerebrovascular amyloid deposits and neurofibrillary tangles also increases exposure of cerebral neurones to SAP.

Cerebral A β amyloid is a defining feature of AD, is also often present in Lewy body dementia (LBD) and is present in chronic traumatic encephalopathy. It is still not known how amyloid pathology contributes to neurodegeneration but recent reports of cognitive benefit from antibody treatments that reduce the A β amyloid burden in AD are encouraging [11,12]. Typical AD neuropathology is often seen in the brains of individuals who were cognitively normal at death, raising the possibility of other pathogenetic factors in dementia. It is therefore interesting that, unrelated to its contribution both to A β amyloid formation and persistence, human SAP is itself directly neurotoxic to cerebral neurones *in vitro* [13–16] and in animal models *in vivo* [17]. Furthermore, neocortical SAP content is significantly associated with dementia at death, independently of neuropathological severity, consistent with a more direct, amyloid-independent, pathogenetic role of SAP in neurodegeneration [18]. Indeed, many of the risk factors for dementia, including cerebral and cerebrovascular amyloid deposition, traumatic brain injury, cerebral haemorrhage and even ‘normal’ ageing, with its associated impairment of the BBB [19], are characterized by increased exposure of the brain to SAP.

In order to rigorously explore the potential causative role of human SAP in human neurodegenerative diseases, and thus validate novel therapeutic avenues, we have now sought genetic epidemiological evidence. SAP is encoded by the gene *APCS* (ENSG00000132703) located on chromosome 1, in close proximity to *CRP* (ENSG00000132693) which encodes C-reactive protein (CRP). These two proteins comprise the pentraxin family, sharing 54% strict residue for residue amino acid sequence homology, even higher genetic sequence homology and having the same secondary, tertiary and quaternary structural organization. Despite notable phylogenetic conservation of gene and protein sequence and structure among pentraxins, there are marked biological differences between these proteins both within and between species [20]. Thus, human CRP is the classical acute phase protein that is among the most commonly used routine clinical chemistry analytes, while human SAP is a constitutive plasma protein, the assay of which has hitherto had no practical clinical significance. Human SAP is not an acute phase reactant although in chronic inflammatory conditions, in which there is sustained increased production of CRP, SAP values tend to be slightly higher, albeit within the reference range [21]. A few small studies in the elderly and subjects with impaired cognition have reported plasma and CSF SAP concentrations above the reference range of the healthy middle-aged population [2,22–24]. Children under 10 years have circulating SAP concentrations below the adult range but reduced adult SAP values are seen only with severe hepatocellular impairment [21]. Unsurprisingly therefore, in contrast to CRP concentration, there have only been limited genome-wide association studies (GWAS) of plasma SAP concentration [24–26]. Recently, however, the SomaLogic aptamer-based proteomic platform has enabled large-scale measurement of circulating SAP abundance, allowing for a growing number of GWAS identifying potential genetic instruments for plasma SAP concentration.

Cis-Mendelian randomization (MR) leverages genetic instruments associated with protein concentration to demonstrate the possible causal effects of a potential drug target and thus to anticipate safety and efficacy outcomes of specific therapeutic interventions. The random allocation of genes during gametogenesis crucially protects genetic associations against bias due to confounding and reverse causality [27,28]. Furthermore, through a two-sample design, MR can source aggregated data, that is, point estimates and standard errors, from large-scale studies, each designed to maximize the available sample size. This extensively validated MR approach can provide a precise and powerful overview of the likely causal consequences of target perturbation covering a large number of clinically relevant diseases and traits [29–32].

We confirmed that the SomaLogic SAP values reliably reflect the actual plasma concentration of the protein measured by rigorously calibrated SAP immunoassay. We then conducted a meta-analysis of three GWAS of circulating SAP values, combining information from 44 288 participants, followed by a drug target MR using *APCS cis*-variants that were strongly associated with plasma SAP values. We primarily focused on the possible causal effect of SAP in AD and LBD. Given the close proximity of *APCS* to *CRP*, and the major involvement of CRP responses with almost all inflammatory, infective, traumatic and other tissue damaging processes [33], we additionally used MR to rule out possible effects of plasma CRP concentration acting on the SAP signal through linkage disequilibrium (LD) between variants in *APCS* and variants in *CRP*.

2. Material and methods

2.1. Validation of SomaLogic SAP assay

The read out from the SomaLogic aptamer-based mass spectrometric method is relative reagent intensity, a proxy for SAP concentration rather than actual mass per volume. We therefore used the robust electroimmunoassay method, rigorously standardized with isolated, pure human SAP [1], to measure the actual concentration of SAP in 100 human plasma samples from a random sub-cohort of the EPIC-Norfolk study (<https://www.epic-norfolk.org.uk/>) in which SAP had been quantified by the SomaLogic method. The electroimmunoassay confirmed that the SomaLogic results accurately reflected plasma SAP concentrations: for the two sets of results, the Pearson correlation coefficient was 0.86 ($p < 0.001$) and Spearman correlation was 0.84 ($p < 0.001$) (electronic supplementary material, figure S1).

2.2. Genome-wide association studies of SAP plasma values

Three independent studies with plasma SAP values determined by the SomaLogic method: Interval (n : 3301) [24], AGES (n : 5368) [26] and DECODE (n : 35 559) [25], were used to provide aggregate genetic data. To account for potential heterogeneity in genetic associations, due to difference in participants and/or environment, we performed a DerSimonian–Laird random effects meta-analysis using METAL [34].

Independent lead genetic variants were identified by filtering associations on a genome-wide significant p -value of 5.8×10^{-8} and clumping to an R^2 of 0.01 based on LD reference data from a random 5000 participant subset of the UK Biobank (UKB). The nearest protein-coding genes were identified by querying the GRCh37 assembly via Ensembl REST API [35]. Lead variants within 2 megabase pairs (MB) of *APCS*, the gene encoding SAP, were assigned to this gene; *trans*-variants (outside ± 2 MB of *APCS*) were mapped to putative causal genes using the V2G algorithm offered by Open Targets [36]. The V2G algorithm ranks putative causal genes based on integrated information on molecular traits, such as information on splice-sites, mRNA expression, chromatin interaction, functional predictions, and distance from the canonical transcription start site. Potential pleiotropic associations of these putative causal genes were explored by querying the author-assigned gene in GWAS Catalog, which comprises the largest source of gene to phenotype information [37].

2.3. Drug target Mendelian randomization

Drug target MR was employed to ascertain the possible causal effects that a unit increase in standard deviation (SD) of plasma SAP concentration had on clinically relevant traits, with a primary focus on AD [38] and LBD [39].

To limit the potential for bias due to pre-translational horizontal pleiotropy, variants were extracted from within and around *APCS*, applying a ± 1 MB pairs flank [40]. Variants were filtered to a minor allele frequency of 0.01 or larger, and clumped to an R^2 of 0.40. Residual LD was modelled using generalized least square (GLS) solutions [41] and a 5000 random sample of UKB participants. To reduce the risk of weak-instrument bias [42], we selected genetic variants with an F-statistic of 15 or higher. Furthermore, due to the absence of sample overlap between the SAP GWAS dataset and the GWAS used for many of the outcome traits, any potential weak-instrument bias would act towards a null effect, reducing power rather than increasing type 1 errors [42,43].

Estimates of the potential causal effect of higher plasma SAP value were obtained using the GLS implementation of the inverse-variance weighted (IVW) estimator and the MR-Egger estimator, the latter being unbiased in the presence of horizontal pleiotropy at the cost of lower precision [44]. To minimize the potential influence of horizontal pleiotropy, variants beyond three times the mean leverage or an outlier χ^2 statistic larger than 10.83 were pruned [45]. Finally, a model selection framework was applied to select the most appropriate estimator, IVW or MR-Egger [45,46]. This model selection framework [47] uses the difference in heterogeneity between the IVW Q-statistic and the Egger Q-statistic to decide which method provides the best model to describe the available data and hence optimizes the bias–variance trade-off.

Given the close proximity of *CRP* to *APCS*, we additionally conducted an MR analysis of CRP concentration, taking advantage of availability of the largest CRP GWAS conducted to date [48]. The MR effect estimates of SAP and CRP were compared to identify outcomes which seemingly were affected by both proteins using a p -value of 0.05. For the subset of outcomes which seemed to be affected by both SAP and CRP, we additionally conducted MVMR to analytically control any influence of CRP on the SAP signal and vice versa. MVMR is similar to standard multiple regression, where multiple variables, in our case two, are included in the same model, resulting in estimates that are mutually independent of one another [49]. Importantly, MVMR allowed us to account for any horizontal pleiotropy that might act through CRP concentration [49]. In addition, to correct for any potential remaining horizontal pleiotropy acting through non-CRP pathways, we applied the same model selection framework to decide between MVMR with and without Egger correction. Where relevant, we differentiate between MVMR and regular MR results by referring to the latter as univariable MR.

2.4. Effect estimates and multiple testing

Unless otherwise specified, all point estimates, that is, odds ratios (OR) or mean differences, refer to a unit change of the independent variable, typically one SD in plasma protein value for MR results or an increase in number of risk alleles for GWAS results, respectively. Results are provided with 95% confidence intervals (CI) and p -values. Significance in the GWAS analysis was evaluated using the standard multiplicity corrected alpha, that is, the false positive rate, of 5.8×10^{-8} , accounting for the estimated number of independent genetic variants in the genome [50]. The MR results were tested against a Bonferroni corrected alpha of 2.78×10^{-3} , accounting for the 18 evaluated traits (Data availability section).

3. Results

3.1. Genome-wide meta-analysis of plasma SAP values

Genetic variant-specific estimates of the association with SAP values, measured by SomaLogic SomaScan assay version 4.1, were available from three independent studies: Interval, comprising 3301 participants [24]; AGES, with 5368 [26]; and DECODE, with 35 559 [25]. The combined data identified 10 independent lead variants associating with SAP, including four *cis*-variants near *APCS* (rs140308485, rs13374652, rs1341664 and rs78228389), as well as *trans*-variants on chromosomes 1, 2, 8 and 13 (figures 1 and 2; electronic supplementary material, table S1). Comparison of the genetic associations with plasma SAP and CRP values in the

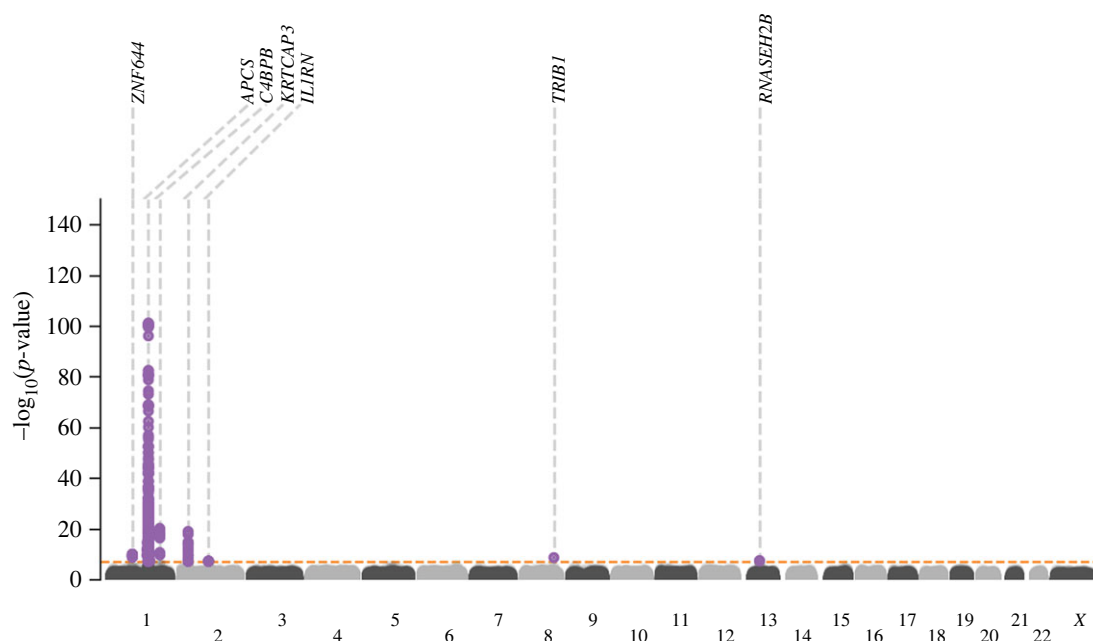


Figure 1. Manhattan plot of SAP genome-wide association study. The $-\log_{10}(p\text{-value})$ of genetic variants is shown on the y-axis and GRCh37 base pair position within chromosomes on the x-axis. The horizontal dashed line is at $p\text{-value } 5.8 \times 10^{-8}$. The lead variants are labelled with the putative causal genes assigned by V2G.

region around rs1341664, the *APCS* *cis*-variant with the strongest SAP association, indicated that these closely adjacent signals were independent (figure 2); the Pearson correlation coefficient comparing the $-\log_{10}(p\text{-value})$ for each trait was -0.06 , $p\text{-value} < 0.001$. This was further confirmed by noting that the CRP association of the four SAP *cis*-variants did not reach genome-wide significance (electronic supplementary material, table S2), with the $-\log_{10}(p\text{-value})$ for CRP ranging between 0.04 and 6.26. Instead, the CRP signals were concordant with the SAP *trans* signals (electronic supplementary material, figure S2 and table S2).

GWAS Catalog look-ups for the effects of genetic variants in *APCS* identified a previously reported association with white-matter microstructure [51] (electronic supplementary material, figure S3 and table S9). Using Open Target's V2G algorithm the six SAP *trans*-variants were mapped to the putative causal genes: *C4BPB*, *ZNF644*, *IL1RN*, *KRTCAP3*, *TRIB1* and *RNASEH2B* (figures 1 and 3; electronic supplementary material, tables S3–S8). Look-ups for the variants within and around the putative *trans*-genes for SAP provided links with a diverse range of pathophysiology without known connections to SAP biology (electronic supplementary material, figure S3 and table S9).

3.2. *Cis*-Mendelian randomization results for plasma SAP values and dementia outcomes

Cis-MR analysis detected significant associations of higher plasma SAP values with increased risk of dementia outcomes: AD (35 274 cases, odds ratio (OR) 1.07, 95%CI 1.02; 1.11, $p = 1.8 \times 10^{-3}$), and LBD (2981 cases, OR 1.37, 95%CI 1.19; 1.59, $p = 1.5 \times 10^{-5}$) (figure 4; electronic supplementary material, table S10). A similar analysis for plasma CRP values did not identify links with these outcomes (electronic supplementary material, table S10).

3.3. *Cis*-Mendelian randomization results for plasma SAP values and other outcomes

Cis-MR analysis suggested that higher plasma SAP value was associated with increased coronary heart disease risk (OR 1.03, 95%CI 1.01; 1.05), greater total brain volume (0.06 SD, 95%CI 0.02; 0.10), lower systolic blood pressure (SBP) (-0.16 mm Hg, 95%CI -0.26 ; -0.07) and lower diastolic blood pressure (DBP) (figure 5; electronic supplementary material, table S11). By contrast, the MR analysis of plasma CRP values showed a distinct effects profile in which higher CRP concentrations were associated with serum concentrations of hepatocellular enzymes, with osteoarthritis and with total plasma tau concentration (figure 5; electronic supplementary material, table S12).

3.4. Multivariable Mendelian randomization results for outcomes linked to both SAP and CRP

APCS and *CRP* are closely co-located on chromosome 1, potentially challenging the recognition of, and discrimination between, more subtle apparent independent effects. We therefore identified outcomes significant at the more liberal value of $p < 0.05$ for both plasma SAP and CRP values, specifically, total brain volume, plasma total tau concentration and osteoarthritis. Application of multivariable MR (MVMR) to identify the mutually independent effects of both proteins, and accounting for potential influence of LD, then showed that higher values of each increased circulating total tau concentration: (0.06 $\log_2(\text{ng l}^{-1})$, 95%CI 0.03; 0.08) for higher plasma SAP value, and (0.20 $\log_2(\text{ng l}^{-1})$, 95%CI 0.14; 0.25) for higher plasma concentration of CRP. The MVMR analysis did not confirm significant associations for osteoarthritis, and total brain volume (electronic supplementary material, table S13).

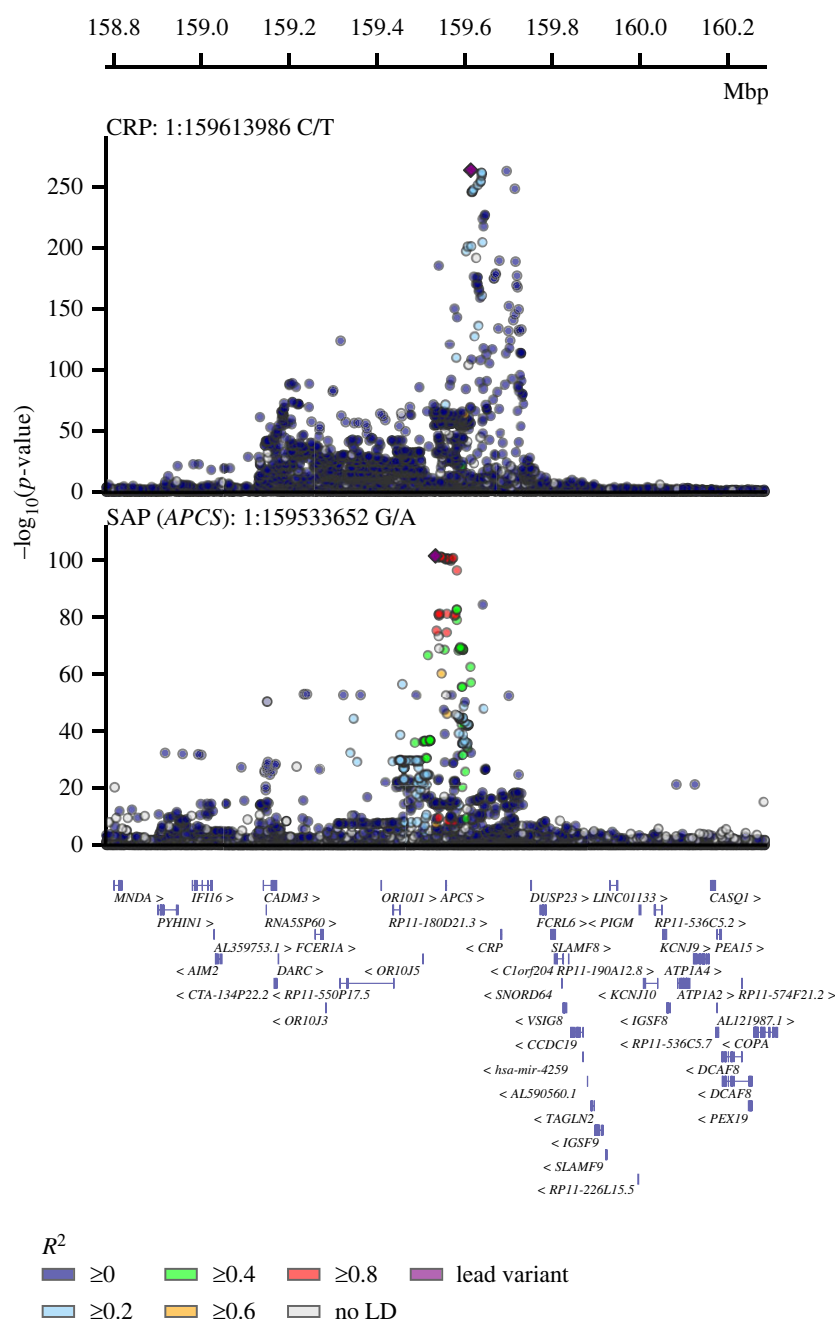


Figure 2. Stacked locus-view comparing the overlap between genetic variants for plasma SAP values and plasma CRP concentration. The $-\log_{10}(p\text{-value})$ of the genetic association with SAP and CRP plotted (y-axis) against the genomic location (x-axis). The lead variant for each trait is indicated by a purple diamond. Linkage disequilibrium with the lead variant is indicated by coloured dots, with the R^2 estimated from the UKB and 1000 genomes EUR reference. Gene locations were queried from Ensembl v109 (GRCh37).

4. Discussion

We report here a large-scale meta-analysis of GWAS of SomaLogic values for plasma SAP comprising 44 288 participants. We confirmed that the SomaLogic intensity scores for plasma SAP agree with immunoassay of actual SAP concentrations. The GWAS results then enabled MR analysis sourcing *cis*-acting variants within and around *APCS*, the gene encoding SAP, to explore potential involvement of SAP in pathogenesis of dementia. We found that higher plasma SAP values increased the risk of AD (OR 1.07, 95%CI 1.02; 1.11, $p = 1.8 \times 10^{-3}$) and LBD (OR 1.37, 95%CI 1.19; 1.59, $p = 1.5 \times 10^{-5}$), implying that pharmaceutical depletion of SAP might reduce the risk of both diseases. Furthermore, using MVMR to account for possible horizontal pleiotropy by plasma CRP concentration, we also detected a significant association of higher plasma SAP values with higher total plasma tau concentration ($0.06 \log_2(\text{ng l}^{-1})$, 95%CI 0.03; 0.08), which is itself also associated with AD dementia [54].

The presence of SAP in all cerebral A β plaques and on most neurofibrillary tangles in AD, long known from immunohistochemical studies, has recently been shown to strongly discriminate between AD brains and cognitively normal brains [55]. However, the present finding of significant associations between genetically determined higher plasma SAP values and increased risk of AD and LBD is more specifically consistent with the association between neocortex SAP content and cognitive status at death that was recently observed in the Cognitive Function and Ageing Study [18]. In this unselected, population-representative, elderly brain donor population, the OR for dementia at death, between the top tertile and the lowest tertile of neocortical SAP

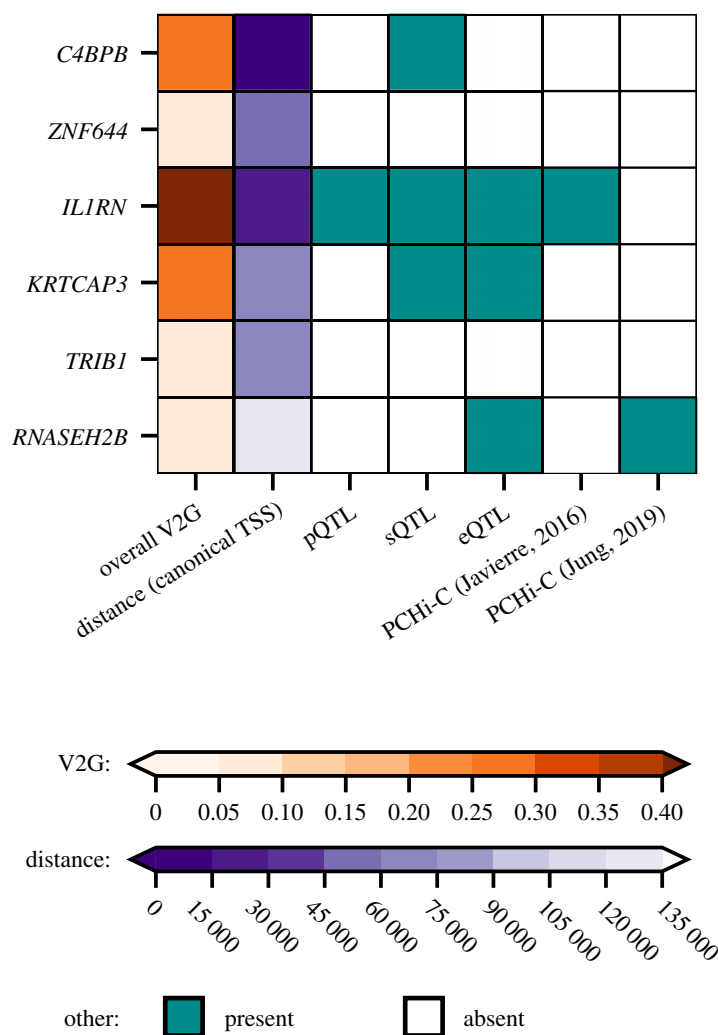


Figure 3. Mapping of the *trans* signals for variants associated with plasma SAP value to putative causal genes. First column, the overall V2G score; second column, distance in base pairs from the lead variant to the canonical gene transcription start site (TSS). The other columns show the presence or absence of *x*-axis criteria, specifically, whether there were quantitative trait loci (QTL) linking the gene to proteomics, transcriptomics, or splice site QTL, and PCHi-C (promoter capture Hi-C) chromatin interaction experiments linking the genetic variant to the indicated gene, from Jung *et al.* [52] and Javierre *et al.* [53]. Electronic supplementary material, tables S3–S8, show the whole V2G output.

content, was 5.24 (95%CI 1.79; 15.29). Furthermore, the association of dementia with SAP content was independent of Braak stage, Thal phase and all other classical neuropathological hallmarks of dementia [18]. It was thus specific for abundance of SAP itself in the neocortex rather than SAP content just being a surrogate for the A β amyloid and neurofibrillary tau tangle pathology which is always present in AD and also frequently found in LBD. This SAP–dementia association, which is consistent with a possible pathogenetic role of SAP in neurodegeneration, is now directly supported by the present MR results.

In contrast to a previously reported MR study, which did not detect an association between SAP values and AD [56], our analysis was improved in multiple ways. First and foremost, instead of simply taking a single SAP GWAS, we meta-analysed combined data from three independent studies to produce the largest GWAS of SAP values to date. This resulted in an AD MR analysis using 53 SAP variants instead of the 14 used by Yueng *et al.* [56]. The larger number of variants allowed us to consider outlier and leverage statistics, identifying and removing variants with possible horizontal pleiotropic effects, further ensuring the robustness of the present findings. Furthermore, we performed confirmatory analyses to refute possible bias due to the location of the *CRP* gene closely adjacent to *APCS*, and we found no meaningful overlap between the effect profiles of plasma SAP and CRP values. Similar to the analysis by Yueng *et al.* [56], we conducted a two-sample MR analysis, where the exposure GWAS did not, or only partially, overlap with the outcome GWAS. Any potential weak instrument bias will thus, on average, act towards a null effect, hence our results are conservative. This, however, also implies that non-significant findings should not be over-interpreted as providing proof of absence [57]. Compared to the Yueng *et al.* [56] analysis, we have expanded our analysis to show an association between SAP value and LBD. Uniquely, the LBD cases were autopsy confirmed [39] and hence this MR result represents a biologically homogeneous disease signal. We wish to emphasize the conducted MR analyses leverage instruments within and around the SAP encoding gene, *APCS*, limiting the potential for horizontal pleiotropy. This was further addressed through removal of potential outlier variants which may reflect horizontal pleiotropy pathways, and additionally we applied statistical methods robust against potential remaining pleiotropic variants. These methods are able to account for between-variant correlation [41], preventing erroneously small *p*-values—similar to the results one obtains using methods such as COJO [58]. Finally, we note that, under the null hypothesis and accounting for the number of evaluated outcomes, the probability of finding an effect of plasma SAP value on AD

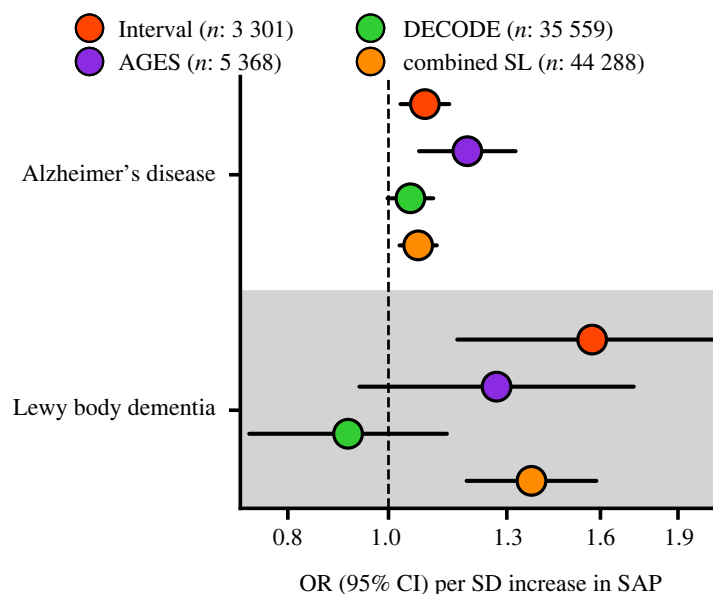


Figure 4. Estimates of the *cis*-Mendelian randomization effect of plasma SAP values on Alzheimer's disease and Lewy body dementia. The univariable MR effects estimated from the GWAS meta-analysis of SomaLogic (SL) plasma SAP values from the Interval, AGES and DECODE studies are shown individually, together with the combined result of all three studies. We used the Alzheimer's disease GWAS from Kunkle *et al.* [38] which consisted of 35 274 cases and 59 163 controls, the Lewy body dementia GWAS from Chia *et al.* [39] consisted of 2981 cases and 2173 controls. OR, odds ratio; 95%CI, 95%CI. The figure illustrates the data in electronic supplementary material, table S10.

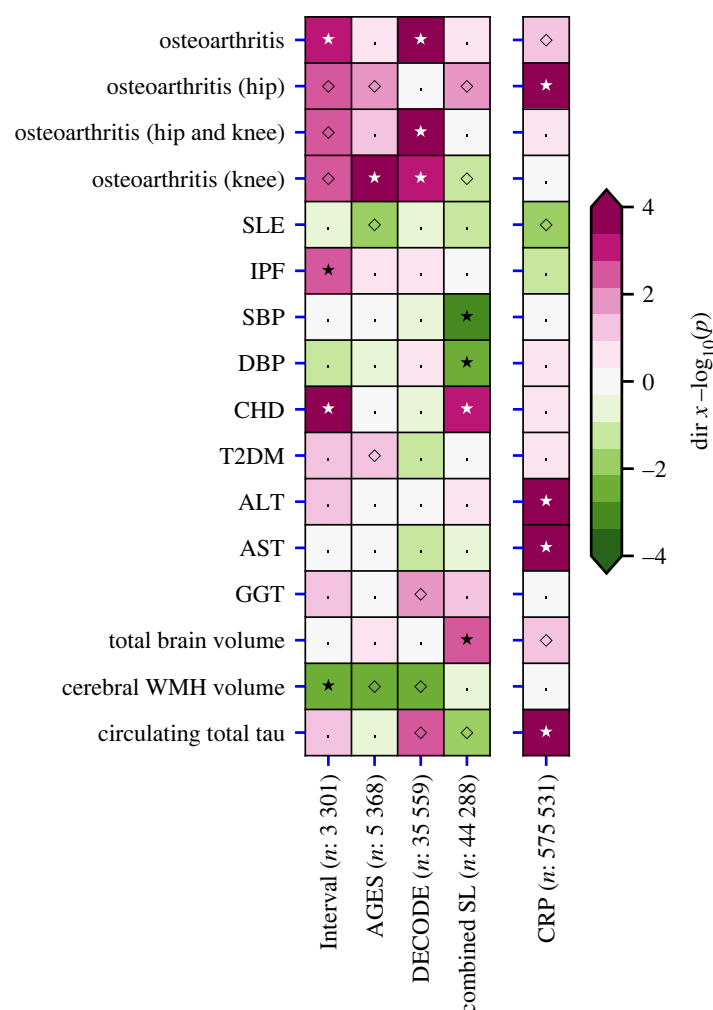


Figure 5. Comparison of the *cis*-Mendelian randomization effect estimates of plasma SAP values and CRP concentration. Effect direction, magenta for positive and green for negative, is shown by the $-\log_{10}(p\text{-value})$. Open diamonds, $p < 0.05$; closed stars, $p < 2.78 \times 10^{-3}$. Left block, SAP; right column, CRP. ALT, alanine transaminase; AST, aspartate transaminase; CHD, coronary heart disease; DBP, diastolic blood pressure; GGT, gamma-glutamyl transferase; IPF, idiopathic pulmonary fibrosis; SBP, systolic blood pressure; SLE, systemic lupus erythematosus; T2DM, type 2 diabetes; WMH, white matter hyperintensities. The figure illustrates the data in electronic supplementary material, tables S11–S12.

as well as on LBD is equal to the square of the alpha: $(2.78 \times 10^{-3})^2 = 7.73 \times 10^{-6}$. The concordant findings thus strongly imply that SAP contributes to pathogenesis of dementia.

Increased duration and/or intensity of brain exposure to SAP may be pathogenic through its direct cytotoxicity for some cerebral neurones, as has been demonstrated experimentally *in vitro* and *in vivo* [13–16], and potentially also by promoting the formation and the persistence of A β amyloid fibrils and neurofibrillary tau tangles. However, SAP is produced only by the liver; it is not in the brain transcriptome [59]. Normally, the brain is strongly protected against exposure to SAP by the BBB and by active transport back to the plasma of any SAP that leaks through [4], so that the CSF SAP concentration is about one thousandth of that in the plasma [2,3]. It is therefore striking that even modestly higher plasma SAP concentrations are associated with dementia risk. There have been very few studies of SAP concentration in paired samples of plasma or serum and CSF but in addition to the circulating SAP concentration, BBB integrity and the efficiency of the SAP active export mechanism must affect brain exposure to SAP. Nevertheless, across the large populations studied here, there was a significant effect of higher plasma SAP concentration on clinical dementia outcomes.

In addition to the four *cis*-loci, our GWAS results identified variants mapping to genes outside *APCS*, including *C4BPB*, *ZNF644*, *IL1RN*, *KRTCAP3*, *TRIB1* and *RNASEH2B*. SAP binds specifically to C4-binding protein, encoded by *C4BPB*, under particular experimental conditions *in vitro* [60], though no functional effect of the interaction has been reported. *IL1RN*, which encodes the IL-1 receptor antagonist (IL-1RA) might have a functional effect on SAP via the acute phase response, which is mediated by IL-1 both directly and via other pro-inflammatory cytokines. Even though human SAP is not an acute phase reactant, its concentration does tend to rise modestly within the reference range in chronic inflammatory diseases with a sustained acute phase response [21]. *TRIB1* has diverse, wide ranging effects across many different physiological systems.

The putatively mapped SAP *trans*-genes have previously been variously linked to a broad range of different metabolic, cardiac and haematological traits and to increased plasma concentrations of liver enzymes. Inclusion of these traits in our *cis*-MR analysis identified an association of higher SAP values with increased coronary heart disease risk and decreased SBP and DBP, but, since there is no known functional connection between these cardiovascular features and SAP, the protein itself is unlikely to be directly involved. Potential pathogenetic connections have been suggested between SAP and two different, unrelated diseases, osteoarthritis [61] and systemic lupus erythematosus [62]. Plasma SAP concentrations were not strongly associated with lupus but there were apparent associations between increased SAP values and some osteoarthritis outcomes (figure 5), perhaps reflecting our conservative analyses. We also found a significant positive association between SAP and idiopathic pulmonary fibrosis, suggesting that SAP may also have a pathogenetic role in this condition (figure 5). By contrast, osteoarthritis [63] and lupus [64], respectively, have well-established positive and negative clinical links with CRP, and, interestingly, both were associated with circulating CRP concentrations in the corresponding directions in the current analysis (figure 5).

Potential limitations to our study comprise, firstly, our use of SomaLogic values for plasma SAP, which are only relative intensities not actual SAP concentrations. SomaLogic assays alone therefore cannot enable precise determination of the effect magnitude relevant for potential pharmaceutical intervention, even though we rigorously demonstrated that the SomaLogic values are in acceptably close agreement with the actual SAP concentrations measured by precise, rigorously standardized electroimmunoassay.

Secondly, previous GWAS of AD and other types of dementia have not reported *APCS* as a potential gene for disease onset. However, GWAS is deliberately designed to limit detection of false positive results and may accordingly leave additional signals undiscovered [27]. It is therefore important to emphasize that drug target MR does not require the GWAS data used for the outcome trait to reach GWAS significance [28].

Thirdly, to prevent potential bias due to population stratification (i.e. where spurious genetic associations are detected due to inclusion of subpopulations with distinct allele frequencies and outcome frequencies) our analysis exclusively used data from people of European ancestries. While this partially mitigates the potential for population stratification, people of European descent of course do not represent a homogeneous genetic population. Hence, to further address this, the SAP GWAS meta-analysis was conducted using an additive random effects method which accounts for heterogeneous effects potentially reflecting differences in underlying biology.

Furthermore, to identify results which may be affected by residual population stratification effects, we conducted study specific MR analyses (leveraging genetic instruments for each individual SAP GWAS), as well as using the meta-analysed SAP GWAS. Focusing specifically on potential difference between the two Icelandic studies (DECODE and AGES) and the British Interval study, we did not observe results which were driven by a single population (see figures 4 and 5). Similarly, we note that the SAP meta-analysis GWAS showed a clear *cis* signal for *APCS*, the gene encoding SAP protein, and limited *trans* signals. We additionally were able to map these *trans* signals to genes with a plausible association with SAP values, providing further empirical support for the limited influence of potential residual population stratification.

Finally, while the present results imply that SAP depletion might reduce dementia risk, they do not indicate optimal timing for the intervention. Neuropathological changes are well known to long precede clinically detectable cognitive loss in AD and other dementias, so SAP depletion might be most effectively introduced prophylactically. Nevertheless, in view of the present evidence for a causal relationship between increased circulating SAP and risk of dementia, prompt SAP depletion may protect residual cognition at any stage.

Fortunately, the experimental drug miridesap (CPHPC; hexanoyl bis-D-proline; (R)-1-[6-[(R)-2-carboxypyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid) [65] safely provides extremely effective SAP depletion. It reduces plasma SAP concentration by more than 95% for as long as the drug is administered [66] and thereby removes all detectable SAP from the CSF in patients with AD [3] and from the brain in human SAP transgenic AD model mice [67]. DESPIAD, a small, academic, phase 2b clinical trial of SAP depletion by miridesap in established AD, is now in progress (EudraCT number 2016-003284-19) and will report in 2025. Meanwhile, our present genetic analysis indicates that depletion of plasma SAP is expected to decrease the risk of AD and LBD.

4.1. Opening up

Without comprehensive elucidation of the mechanisms directly responsible for the neurodegeneration underlying most common forms of dementia, devising and developing new disease modifying therapeutics have had little success. Our present MR study is the genetic counterpart of a large-scale, placebo controlled, double blind, therapeutic drug trial. It has provided two clear new messages. Firstly, there is strong, independent, genetic evidence that SAP plays a causal role in pathogenesis of AD and LBD, thereby validating previous substantial observational studies consistent with such a role of SAP. Secondly, our unique genetic result validates and encourages therapeutic testing of SAP depletion in these dementias and in conditions predisposing to them. Very importantly, therapeutic SAP depletion is already available. The experimental small molecule drug miridesap very effectively, potently and safely, depletes SAP from the blood and thereby removes all SAP from the CSF in AD patients and from its binding to cerebral deposits of human A β amyloid in transgenic AD model mice. The demographic explosion of dementia in ageing populations worldwide urgently demands optimized clinical trials of SAP depletion. Despite being notoriously slow and expensive, clinical trials in AD will be essential and on a much larger scale than the DESPIAD exploratory trial that will report in 2025. Meanwhile, traumatic brain injury, which strongly predisposes to early onset dementia, is an attractive, potentially earlier outcome, trial target. We have lately confirmed that there is abnormal, excess, entry and persistence of SAP, specifically localized in/on some neurones and their processes, in contused brain after such injury [68]. In contrast to the decades of pre-clinical, prodromal, neuropathology in AD and LBD, the timing of traumatic brain injury is usually precisely known and swift medical intervention will enable immediate SAP depletion. Whether this is clinically neuroprotective will be of considerable interest.

Ethics. This work did not require ethical approval from a human subject or animal welfare committee.

Data accessibility. The SAP GWAS meta-analysis results have been deposited on figshare (rs.figshare.com). The same figshare repository also contains the data used in the Mendelian randomization analysis, including genetic associations with the 17 clinical traits. Specifically, we leveraged data on SAP plasma value from DECODE (<https://download.decode.is/form/folder/proteomics>), AGES (<https://doi.org/10.5281/zenodo.5711426>) [69] and Interval (<https://www.ebi.ac.uk/gwas/studies/GCST90242796>). Data on CRP concentration were obtained from: <https://www.ebi.ac.uk/gwas/studies/GCST90029070>. GWAS data were accessed for the following traits: Alzheimer's disease (<https://www.niagads.org/>, from Kunkle *et al.*), Lewy body dementia (<https://www.ebi.ac.uk/gwas/publications/33589841>), osteoarthritis (<https://www.ebi.ac.uk/gwas/publications/30664745>), systemic lupus erythematosus (<https://www.ebi.ac.uk/gwas/publications/26502338>), idiopathic pulmonary fibrosis (<https://pubmed.ncbi.nlm.nih.gov/33197388/>), systolic/diastolic blood pressure (<https://www.ebi.ac.uk/gwas/publications/30224653>), coronary heart disease (<https://www.ebi.ac.uk/gwas/publications/36474045>), type 2 diabetes (<http://diagram-consortium.org/downloads.html>, from Mahajan *et al.*), liver enzymes (<https://www.ebi.ac.uk/gwas/publications/33972514> and <https://www.ebi.ac.uk/gwas/publications/33547301>), brain volume (https://ctg.cncr.nl/software/summary_statistics, from Jansen *et al.*), cerebral white matter hyperintensities (<https://www.ebi.ac.uk/gwas/publications/26674333>), circulating total tau values (<https://www.ebi.ac.uk/gwas/publications/35396452>). All data needed to evaluate the conclusions in the paper are present in the paper and the electronic supplementary material [70].

Declaration of AI use. We have not used AI-assisted technologies in creating this article.

Authors' contributions. A.F.S.: conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing—original draft; C.F.: conceptualization, data curation, formal analysis, visualization, writing—review and editing; S.C.: data curation, formal analysis, writing—review and editing; S.E.: data curation, formal analysis, writing—review and editing; M.N.R.: conceptualization, investigation, writing—review and editing; A.D.H.: conceptualization, investigation, writing—review and editing; M.B.P.: investigation, project administration, writing—review and editing.

All authors gave final approval for publication and agreed to be held accountable for the work performed therein.

Conflict of interest declaration. A.F.S. and C.F. have received funding from New Amsterdam Pharma for unrelated work. M.B.P. is the inventor on expired patents on SAP depletion by miridesap (CPHPC). GlaxoSmithKline's abandoned patents on an experimental miridesap prodrug were assigned to UCL spinout company, Pentraxin Therapeutics Ltd, founded and directed by M.B.P; but are no longer maintained. The other authors have no competing interests.

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