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Genetic variants in glutamate, Aβ and tau related pathways determine polygenic risk for Alzheimer's disease

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Declaration of interest: Dr Belbin declares a patent application for Markers of Synaptopathy in Neurodegenerative Disease (WO2019175379; pending). The patent does not relate to data included in this study.

Abstract

Synapse loss is an early event in late-onset Alzheimer's disease (LOAD). In this study we have assessed the capacity of a polygenic risk score (PRS) restricted to synapse-encoding loci to predict LOAD. We used summary statistics from the IGAP genome-wide association meta-analysis of 74,046 subjects for model construction and tested the "Synaptic PRS" in two independent datasets of controls and pathologically-confirmed LOAD. The mean Synaptic PRS was 2.3-fold higher in LOAD compared to controls ($p<0.0001$) with a predictive accuracy of 72% in the target dataset (n=439) and 73% in the validation dataset (n=136), a 5-6% improvement compared to the *APOE* locus ($p<0.00001$). The model comprises 8 variants from 4 previously-identified (*BIN1*, *PTK2B*, *PICALM*, *APOE*) and 2 novel (*DLG2*, *MINK1*) LOAD loci involved in glutamate signaling ($p=0.01$) or APP catabolism/tau binding ($p=0.005$). As the simplest PRS model with good predictive accuracy to predict LOAD, we conclude that synapse-encoding genes are enriched for LOAD risk-modifying loci. The Synaptic PRS could be used to identify individuals at risk of LOAD before symptom onset.

Keywords

Polygenic risk score; late-onset Alzheimer's disease; glutamate signaling; Aβ; tau

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AD; Alzheimer's disease, BDR; Brains for Dementia Research, FDR; false discovery rate, GWAS; genome-wide association studies, IGAP; International Genetics of Alzheimer's project, LD; linkage disequilibrium. LOAD; late-onset AD. PRS; polygenic risk scores, SNPs; single nucleotide polymorphisms.

1. Background

The genetic component of early–onset familial AD is attributed to genetic variants in the *APP*, *PSEN1* and *PSEN2* genes, all of which are central to the amyloid cascade hypothesis (Hardy and Selkoe, 2002). The most prominent late-onset AD (LOAD) risk locus (*APOE*) was detected almost 30 years ago (Pericak-Vance, et al., 1991). The ε4 allele of *APOE* confers a 3-fold increased risk for AD in heterozygous carriers increasing to up to 12-fold in the homozygous state (Corder, et al., 1993). The development of single nucleotide polymorphism (SNP) arrays has enabled genome-wide association studies (GWAS) of increasing sample size followed by meta-analyses of multiple datasets to discover many new AD associated loci. In 2019, The International Genetics of Alzheimer's project (IGAP) reported the largest meta-analysis of case-control studies (over 80,000 subjects) so far (Kunkle, et al., 2019). Additionally, several rare variants have been characterized by next generation sequencing approaches. Collectively, these approaches have led to the identification of over 40 loci that modify the risk of AD (de Rojas, et al., 2019,Guerreiro, et al., 2013,Harold, et al., 2009,Jonsson, et al., 2012,Jonsson, et al., 2013,Lambert, et al., 2013,Seshadri, et al., 2010,Sims, et al., 2017). However these signals cannot not explain the entire genetic component of LOAD and suggest a substantial 'missing heritability' (Ridge, et al., 2016).

One concept that has been gaining traction more recently is the idea that the combined effect of many loci of smaller effect, both common and rare, in addition to the currently known AD associated variants might explain some of the missing genetic risk (Purcell, et al., 2009). This effect can be estimated by generation of a polygenic risk score (PRS) (Abraham and Inouye, 2015,Escott-Price, et al., 2015,Torkamani, et al., 2018). Several studies have reported PRS with good accuracy to predict LOAD (Chaudhury, et al., 2018,Tan, et al., 2018,Tan, et al., 2017,van der Lee, et al., 2018) or conversion from mild cognitive impairment (Adams, et al., 2015,Chaudhury, et al., 2019,Rodriguez-Rodriguez, et al., 2013). That being said, these PRS are typically comprised of hundreds or even thousands of loci, thereby limiting their utility as an early screening tool to identify individuals at high-risk for developing AD. Restricting PRS to loci implicated in pathways central to LOAD pathogenesis, could lead to simpler PRS models. As synapse loss is an early event in AD (Selkoe,

2002) and the best pathological correlate for cognitive decline (Terry, et al., 1991), we hypothesized that variability in genes that encode proteins integral to synaptic function may be enriched for genetic variants with small effect size, whose cumulative effect may have high predictive capacity for identifying individuals susceptible to LOAD.

In this study we have used summary statistics from a large reference GWAS dataset (74,046 subjects) to determine the optimal PRS restricted to synaptic loci (henceforth termed, Synaptic PRS). We have determined the predictive capacity of the Synaptic PRS in two datasets of cognitively normal controls (target dataset; n=137, validation dataset; n=80) and pathologically confirmed LOAD patients (target dataset; n=302, validation dataset; n=56) from the Brains for Dementia Research (BDR) resource. Furthermore, we have compared the predictive capacity to that of a previously reported PRS comprising the top genome-wide association loci on the Neurochip platform (Neurochip PRS) (Lleo, et al., 2019).

2. Methods

2.1. Patient Samples

Experimental procedures were approved by local ethics committees - Nottingham Research Ethics Committee 2 (REC reference 04/Q2404/130); London – City and East NRES (REC reference 08/H0704/128+5) and completed in accordance with approved guidelines. All donors gave written informed consent as governed by local guidelines. The DNA samples used in this study were extracted from autopsied brain tissue prospectively selected from Batch 1 and 2 (target dataset) and Batch 3 (validation dataset) from the BDR resource (Brookes, et al., 2018). Samples recruited for the control group were from cognitively normal subjects with a clinical dementia rating of 0 (target dataset; n=137, validation dataset; n=80). LOAD patients had a clinical diagnosis of dementia due to AD and neuropathological confirmation of AD pathology (target dataset; n=302, validation dataset; n=56).

2.2. Sample preparation and genotyping

DNA from the BDR resource was extracted using a standard phenol chloroform method on 100mg of brain tissue. DNA quality was assessed using the Agilent 2200 TapeStation DNA Integrity Number (mean=8.95) and quantified using Nanodrop 3300 spectrometry. Genotyping of 486,137 variants on the target dataset was performed on the customized NeuroChip array (Blauwendraat, et al., 2017). Quality control was completed using GenomeStudio2.0 (Illumina) and PLINK1.9 (Chang, et al., 2015). Specifically, genotype clustering was completed with the assistance of a cluster file provided by Blauwendraat and colleagues (Blauwendraat, et al., 2017), further QC was based on low GenTrain score, low cluster separation score and low call rate (all < 0.5 in GenomeSudio). The target dataset was aligned to the GRCh37/hg19 assembly in PLINK using files provided by Rayner, W (Personal correspondence, Nov 2017). Samples were removed based on call rate (<90%), gender mismatch, deviation from European population parameters and excess heterozygosity (±3 standard deviations from the mean). SNPs were removed from the target dataset based on call rate (<95%) and Hardy-Weinberg equilibrium being greater than the Bonferroni corrected p-value threshold (1×10^{-7}). Following quality control 484,402 SNPs remained. The *APOE* SNPs, rs7412 and rs429358, were genotyped with TaqMan assays using standard protocols. The same procedures were used for the validation dataset.

2.3. GWAS dataset (IGAP)

The β-statistic and p-values for 7,055,881 SNPs across the whole genome were extracted from a reference genome-wide dataset (Stage 1 meta-analysis of GWAS that included 74,046 subjects and was performed under the banner of IGAP (Lambert, et al., 2013). SNPs that lie within the 500kb region surrounding *APOE* (chr19:45160844-45660844; GRCh37/hg19 assembly) were excluded from the raw genotyped data but, since *APOE* was included in the synaptic gene list, the 2 SNPs that confer ε4 status (rs7412 and rs429358) were added back into the final GWAS dataset. There were 262,737 SNPs common to the IGAP data and the NeuroChip.

2.4. Synapse SNP set

We retrieved a list of 537 genes that encode synaptic proteins from the GRCh37/hg19 reference assembly (UCSC genome browser Kent et al., 2002). The list (**Supplementary Table 1**) represents a

conservative estimate of the synaptic proteome, according to criteria described in our previous study (Lleó, et al., 2019) that includes an established synaptic function and detection in synapse-enriched fractions from mouse, rat or human brain tissue. The 17,262 SNPs that lie within the synaptic gene regions were extracted using the PLINK1.9 extract function. SNPs that were not present on the Neurochip or in the GWAS dataset were removed. 227,015 SNPs present in the IGAP data for these 537 genes were not available on the NeuroChip platform. We next applied the "Clumping" algorithm using PRSice-2 to the remaining 9,420 SNPs. This algorithm assigns an index SNP for each linkage disequilibrium (LD) block, defined as the SNP that showed the most significant association with AD (lowest p) in the IGAP sample dataset, and removes SNPs within 250kbp that showed strong pair-wise LD (r^2>0.1) with the index SNP. The 500kb region surrounding *APOE* was removed from the Neurochip dataset but, since *APOE* was included in the synaptic gene list, the 2 SNPs that confer ε4 status (rs7412 and rs429358) were added back into the final synapse SNP set, which consisted of 2,993 SNPs (**Supplementary Table 2**).

2.5. Pathway enrichment analysis

We extracted statistically over-represented biological processes, molecular function and cellular components annotated to the Synaptic PRS loci using the PANTHER online analysis tool (URL: http://www.pantherdb.org (Mi, et al., 2019)). Only ontologies with a false discovery rate (FDR) adjusted p-value <0.05 were imported into Cytoscape v3.71 (Shannon, et al., 2003) for cluster analysis using the ClusterOne function.

2.6. Statistical Analysis

PRS were calculated using PRSice-2 software (Choi and O'Reilly, 2019,Euesden, et al., 2015) as previously described (Chaudhury, et al., 2019). **Figure 1** shows the PRS workflow. An unbiased threshold for p-values associated with the 2,993 SNPs in the GWAS dataset (testing from $p<10^{-6}$ to $p=1$ in increments of 10^{-6}) was used to prioritize SNPs that gave the best fitting PRS model (highest Nagelkerke r^2 value). The β-statistic in the reference dataset was used to generate weighting estimates for each SNP. The weighted contribution of each SNP to the model is expressed as the β-statistic for that SNP / sum of the β-statistic of all SNPs in the model x 100. Empirical p-values were generated

for the association of the model with LOAD over 10,000 iterations to minimize over-fitting (Choi and O'Reilly, 2019,Euesden, et al., 2015). Where specified, we included non-genetic predictors of LOAD (age-at-death and sex) using the covariates parameter in the PRSice-2 software. Mean PRS scores (two-tailed Students T test) and variance in PRS scores (Levene's Test) were compared between LOAD and controls using IBM SPSS Statistics 25 software. We calculated p-values and odds ratios (OR) for association of individual SNPs in the Synaptic PRS model with LOAD using a Fisher's exact association test employed in PLINK1.9. Receiver operating characteristic (ROC) curves were generated in R version 3.5.2 using the PRROC package (Grau, et al., 2015) to determine the accuracy (AUC) of the PRS models to predict LOAD. We used DeLong's test (SPSS) to compare AUC between models.

3. Results

The BDR samples used in the target dataset included 137 controls and 302 pathologically confirmed LOAD patients. The mean age-at-death and male:female ratio were comparable between controls (83.7 years, standard deviation 9.9, 48% female) and LOAD patients (82.9 years, standard deviation 8.5, p=0.4, 50% female, p=0.8). As expected, the percentage of *APOE* ε4 carriers was higher in LOAD patients (~~65~~66%) compared to controls (~~40~~16%, p<0.001).

The optimal threshold for inclusion of SNPs from the restricted synapse SNP set (n=2,993) in the PRS model was $p<10^{-6}$ (Nagelkerke's r^2=0.16, empirical p<0.001). The **Table** shows the individual association of the 8 SNPs that passed this threshold with LOAD both in the IGAP meta-analysis and in the independent BDR samples. The weighted contribution of each individual SNP to the PRS model is also shown. The 8 SNPs are located in 6 genes, of which *APOE* had the greatest contribution (combined weight for rs429358 and rs7412 = 67.8%), followed by *DLG2* (9.9%) and *BIN1* (combined weight for rs35114168 and rs17014923 = 9.4%), whereas *MINK1*, *PICALM* and *PTK2B* all individually contributed <5% weighting to the model. **Figure 2A** shows that the mean PRS was 2.3-fold higher in LOAD compared with controls (p<0.0001) in the target dataset. **Figure 2B** compares the predictive accuracy of the Synaptic PRS with that of 3 other models; the Synaptic PRS + non-genetic factors, the 2 SNPs that confer ε4 status (APOE E4) and the previously described Neurochip

PRS (Chaudhury, et al., 2019), which comprises 167 SNPs + the 2 ε4 status SNPs. The Synaptic PRS predicted LOAD with 72.0% accuracy and was not improved by including non-genetic factors (difference=0.02%, p=0.8). Compared to APOE E4 (67.4%), the Synaptic PRS improved the accuracy by 4.6% (95% CI 2.5 to 6.7, p<0.0001). While the Synaptic PRS showed only a nominal 2.7% improvement (95% CI -1 to 7, p=0.2) over the Neurochip PRS, with 161 fewer SNPs, it represents the simplest PRS model with good accuracy to predict LOAD.

We next tested the predictive capacity of the Synaptic PRS in an independent validation set of BDR samples that included 80 controls and 56 pathologically confirmed LOAD patients. The male:female ratio was comparable between controls (58% female) and LOAD patients (65% female, p=0.3) whereas the mean age-at-death was lower in LOAD (84.5, standard deviation=8.7) compared to controls (88.4, standard deviation=8.0, p=0.008). As expected, the percentage of *APOE* ε4 carriers was higher in LOAD patients (60%) compared to controls (16%, p<0.0001). **Figure 2C** shows that the mean Synaptic PRS was 3.6-fold higher in LOAD compared with controls (p<0.0001) in the validation dataset. **Figure 2D** shows that the Synaptic PRS predicted LOAD with 73.1% accuracy in the validation dataset, similar to the accuracy reported for the target dataset (72%). The predictive accuracy of the APOE E4 and Neurochip PRS in the validation dataset was 49.2% and 50.7%, respectively. However, it should be noted that due to missing genotype data, the Neurochip PRS for the validation dataset comprised 163 SNPs compared to 169 SNPs in the target dataset. Nevertheless, these data show that the Synaptic PRS represents the simplest PRS model with good accuracy to predict LOAD and has been replicated with comparable accuracy in two independent datasets. To determine whether the proteins encoded by the 8 Synaptic PRS loci have a shared function either within, or in addition to, their function at the synapse, we tested for over-represented gene ontologies annotated to the 6 encoded proteins (**Figure 3**). The 6 proteins can be divided into two highly inter-related clusters; Cluster 1 (p=0.01) includes MINK1, DLG2, PTK2B and their shared annotations related to glutamate receptor signaling and ion transport. All 3 proteins within this cluster are annotated to the postsynapse and, specifically to the glutamatergic synapse. Cluster 2 (p=0.005) includes APOE, PICALM, BIN1 and their shared annotations related to APP catabolism

and tau protein binding and cellular component size and synapse. PICALM and BIN1 are annotated to the presynapse, and specifically to the synaptic vesicle. APOE is annotated to the glutamatergic synapse.

4. Discussion

Here we report that a PRS based on 8 SNPs located in 6 genes that encode synaptic proteins shows improved (72.0%) predictive accuracy compared to the *APOE* locus (67.7%) in 137 controls and 302 LOAD patients. Moreover the Synaptic PRS performed similarly to the previously reported Neurochip PRS (69.3%), which includes the 8 SNPs that comprise the Synaptic PRS or a proxy. The predictive accuracy of the Synaptic PRS was replicated (73.1%) in a second, independent dataset of 80 controls and 56 LOAD patients. The elevated age-at-death of controls (88 years) relative to LOAD (85 years) in the validation cohort supports the idea that the Synaptic PRS is a predictor of AD and not normal aging. In summary, by limiting the PRS to just 8 SNPs that lie within synapse-encoding regions, the Synaptic PRS represents the simplest PRS model with good accuracy (72 to 73%) to predict LOAD Using the Synaptic PRS rather than the Neurochip PRS would therefore significantly reduce genotyping costs and allow simpler and faster data processing times with no effect on accuracy of the model. Of the 8 SNPs that form the Synaptic PRS, 2 lie in genes (*MINK1* and *DLG2*) that have yet to be associated with LOAD risk and were only nominally associated with AD in the reference GWAS ($p<1x10^{-5}$). That being said, genetic variation in *DLG2* has been associated with developmental disorders and intellectual disability (Reggiani, et al., 2017) and *MINK1* gene expression is altered in post-mortem AD brains (Broce, et al., 2019). These two SNPs combined accounted for 14.9% of the weighting in the Synaptic PRS model. The remaining 85.1% was contributed by loci that have previously shown replicable association with LOAD (Bertram, et al., 2007), namely *APOE* (67.8% combined weighting), *BIN1* (9.4% combined weighting), *PTK2B* (3.4%) and *PICALM* (4.5%), albeit that the SNPs were not the same as those identified in prior GWAS studies; rs17057043 (*PTK2B*) was in perfect LD ($r^2=1$) with the *PTK2B* SNP (rs28834970) identified previously so likely reflects the same signal whereas *BIN1* (rs17014923, $r^2<0.08$ and rs35114168,

r^2<0.24) and *PICALM* (rs609903, r^2<0.64) SNPs were not in strong LD with previously identified loci.

As reported in our previous study (Lleo, et al., 2019), the proteins encoded by the 6 Synaptic PRS genes are all expressed at the cortical synapse and all have an established synaptic function. Specifically, MINK1 plays a critical role in AMPA receptor function (Hussain, et al., 2010). DLG2 forms a postsynaptic scaffold for the clustering of receptors and ion channels (Nithianantharajah, et al., 2013) and is associated with glutamatergic dysfunction in major depressive disorder (Duric, et al., 2013). PTK2B is involved in glutamatergic signaling and long-term potentiation (Giralt, et al., 2017). APOE plays a role in regulation of synaptic plasticity and AMPA receptor clustering (Valastro, et al., 2001), dendritic spine formation (Nwabuisi-Heath, et al., 2014) and cholinergic sprouting (Bott, et al., 2016). BIN1 is involved in postsynaptic trafficking (Yao, et al., 2010) and glutamatergic signaling (Schurmann, et al., 2019). PICALM is involved in synaptic vesicle maturation (Petralia, et al., 2013). Furthermore, we report here that these 6 proteins can be divided into two highly inter-related clusters enriched for functions associated with APP catabolism, tau protein binding and glutamate signaling, processes that are so fundamental to early AD pathophysiology (Gao, et al., 2018,Hardy and Selkoe, 2002,Wang and Reddy, 2017) that they are the target of drugs currently in ongoing AD clinical trials (Aβ and tau accumulation) or are the target of therapies already prescribed for the treatment of AD symptoms (blockade of NMDA-mediated glutamate signaling). Overall these data support the recently proposed conceptualization of LOAD as a genetically driven synaptic failure (Dourlen, et al., 2019).

4.1. Conclusions

The data reported here lend further support to the hypothesis that polygenic risk may account for some of the missing heritability in AD and that a pathway-targeted approach can result in PRS with high predictive accuracy for a relatively small number of variants. The relative simplicity of the Synaptic PRS without a concomitant drop in predictive capacity supports the hypothesis that synapse-encoding genes are enriched for LOAD risk-modifying loci. While caution should be taken in interpreting these findings until they have been replicated in larger, independent datasets, our

preliminary findings suggest that genetic variation in glutamate signaling, Aβ production and tau-binding pathways may be important contributing factors to LOAD risk. Future studies into the functional relevance of these variants to these early AD pathways could shed further light into the genetic basis underlying their cumulative risk for LOAD and could lead to novel therapeutic strategies. The potential for these 8 polymorphisms as an accurate early screening tool to identify individuals at high-risk for developing AD before symptom onset would also be an interesting avenue worth pursuing.

5. Acknowledgements

We gratefully acknowledge all donors and their families for the tissue provided for this study. Human post-mortem tissue was obtained from the South West Dementia Brain Bank, London Neurodegenerative Diseases Brain Bank, Manchester Brain Bank, Newcastle Brain Tissue Resource and Oxford Brain Bank, members of the Brains for Dementia Research (BDR) Network. We acknowledge the neuropathologists at each centre (the South West Dementia Brain Bank, the Manchester Brain Bank, Newcastle Brain Tissue Resource and the Oxford Brain Bank) and BDR Brain Bank staff for the collection and classification of the samples. We thank Dr William Rayner of The Wellcome Trust of Human Genetics for providing the strand files for alignment of the NeuroChip to the GRCh37 assembly. We also thank the International Genomics of Alzheimer's Project (IGAP) for providing summary results data for these analyses. The investigators within IGAP contributed to the design and implementation of IGAP and/or provided data but did not participate in analysis or writing of this report. IGAP was made possible by the generous participation of the control subjects, the patients, and their families. This work was supported by Alzheimer's Research UK (2809), Center of Network Research in Neurodegenerative Diseases (Centros de Investigación en Red Enfermedades Neurodegenerativas: CIBERNED), the Institute of Health Carlos III (Instituto de Salud Carlos III, Ministerio de Ciencia, Innovación y Universidades - ISCIII, Spain, PI18/00327), the Generalitat de Catalunya (AGAUR: SGR 2017-19) and European Regional Development Fund from the European Union ("A way to make Europe"). OB is also supported by the Miguel Servet Associate Fellowship (ISCIII, CP18/00011). SC was supported by a PhD studentship from the Neurosciences Group at

Queen's Medical Centre (Nottingham) and the School of Life Sciences, University of Nottingham. The BDR is jointly supported by Alzheimer's Research UK and the Alzheimer's Society in association with the Medical Research Council (G0400074). The IGAP resource was supported by the French National Foundation on Alzheimer's disease and related disorders, LABEX (DISTALZ), Inserm, Institut Pasteur de Lille, Université de Lille 2, and the Lille University Hospital, the Medical Research Council (503480), Alzheimer's Research UK (503176), the Wellcome Trust (082604/2/07/Z), the German Federal Ministry of Education and Research (BMBF: 01GI0102, 01GI0711, 01GI0420), the NIH/NIA (R01 AG033193, U01 AG032984, U24 AG021886, U01 AG016976), the NIA (AG081220), AGES (N01-AG-12100), the NHLBI (R01 HL105756), the Icelandic Heart Association, Erasmus Medical Center and Erasmus University and the Alzheimer's Association (ADGC-10-196728). The funders of this study played no role in the design of the study, collection, analysis or interpretation of data or writing the manuscript.

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Table 1. Association of the individual SNPs included in the Synaptic PRS model with LOAD.

Locus					IGAP reference GWAS			Target dataset			Contribution
GENE	**SNP**	**CHR**	**BP**	**Allele**	**MAF (AD;CTRLS)**	**β**	**p-value**	**MAF (AD;CTRLS)**	**OR**	**p-value**	**to model**
BIN1	rs17014923	2	127841930	T	0.16;0.20	-0.1079	$4x10^{-7}$	0.14;0.19	0.8	0.2	4.2%
BIN1	rs35114168	2	127847930	A	0.40;0.32	0.1327	$4x10^{-16}$	0.32;0.28	1.4	0.03	5.2%
PTK2B	rs17057043*	8	27220310	A	0.37;0.44	0.0882	$1x10^{-7}$	0.37;0.41	1.3	0.07	3.4%
PICALM	rs609903	11	85740409	A	0.28;0.33	-0.1141	$6x10^{-12}$	0.24;0.29	0.8	0.1	4.5%
DLG2	rs286043*	11	85072958	C	0.02;0.004	0.2547	$6x10^{-6}$	0.02;0.01	4.6	0.1	9.9%
MINK1	rs8078173*	17	4763551	C	0.10;0.07	0.1279	$3x10^{-6}$	0.09;0.07	1.5	0.1	5.0%
APOE	rs429358	19	45411941	C	0.39;0.19	1.3503	$7x10^{-536}$	0.33;0.18	2.8	$2x10^{-9}$	52.7%
APOE	rs7412	19	45412079	T	0.05;0.08	-0.3871	$1x10^{-22}$	0.05;0.08	0.6	0.05	15.1%

The summary statistics from the IGAP GWAS and Neurochip in the BDR dataset (p-value, OR, MAF) are shown.

*SNPs also included in the Neurochip PRS set (Chaudhury, et al., 2019).

7. Figures

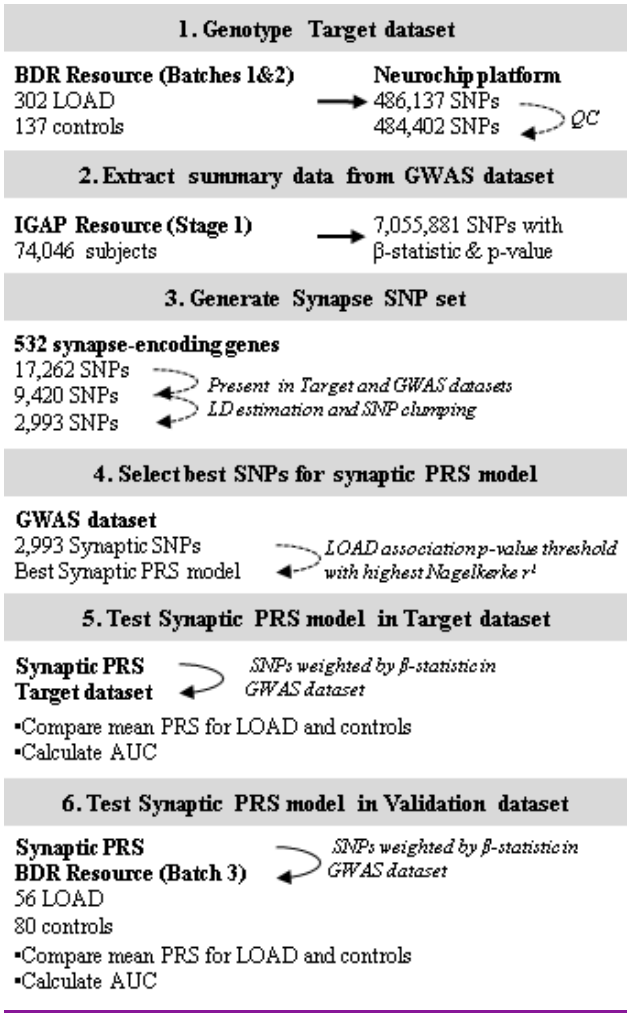

Figure 1. Study design and workflow.

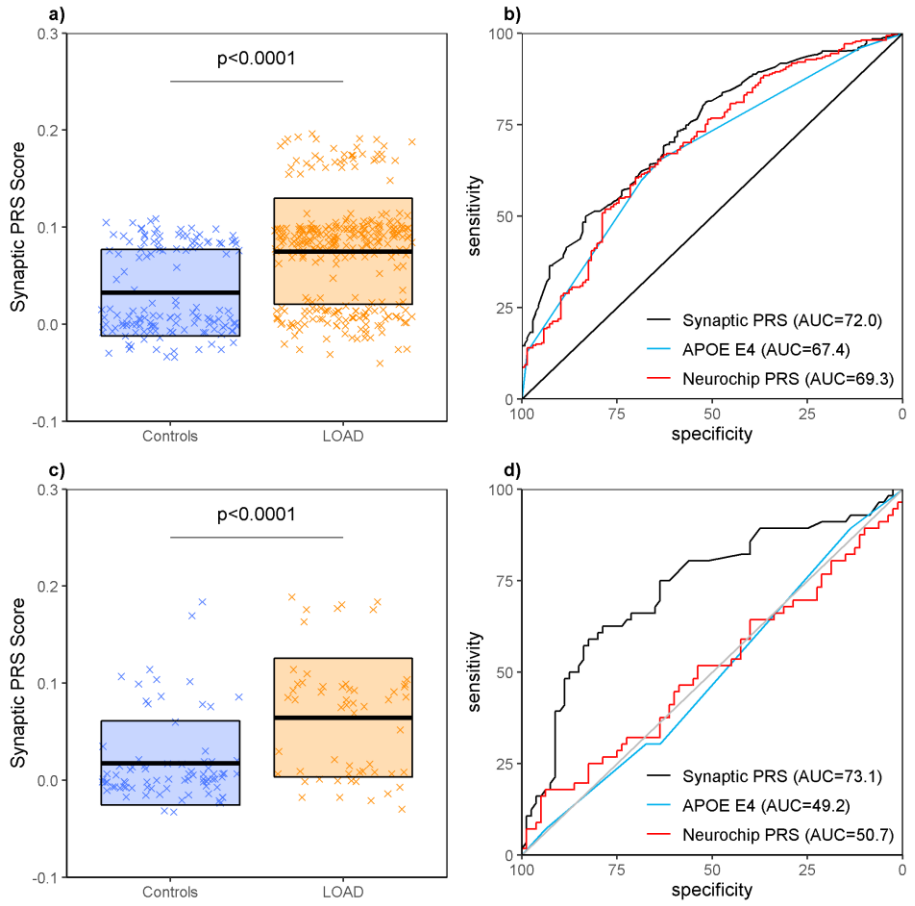

Figure 2. Synaptic PRS model as a predictor of LOAD. ~~a)~~ Mean and standard deviation of the polygenic risk scores for the best predictors from the synaptic gene list (Synaptic PRS) are plotted for the LOAD and healthy controls from the target (**a**) and validation (**c**) datasets. ~~b)~~ ROC curves plot the specificity and sensitivity of the Synaptic PRS and other models (see legend) to classify LOAD and healthy controls in the target (**b**) and validation (**d**) datasets. The Neurochip PRS comprises 169 SNPs for the target dataset and 163 SNPs for the validation dataset. ~~c) Mean and standard deviation of the Synaptic PRS are plotted for the LOAD and healthy controls from the validation dataset. d) ROC curve plots the specificity and sensitivity of the Synaptic PRS to classify LOAD and healthy controls in the validation dataset.~~

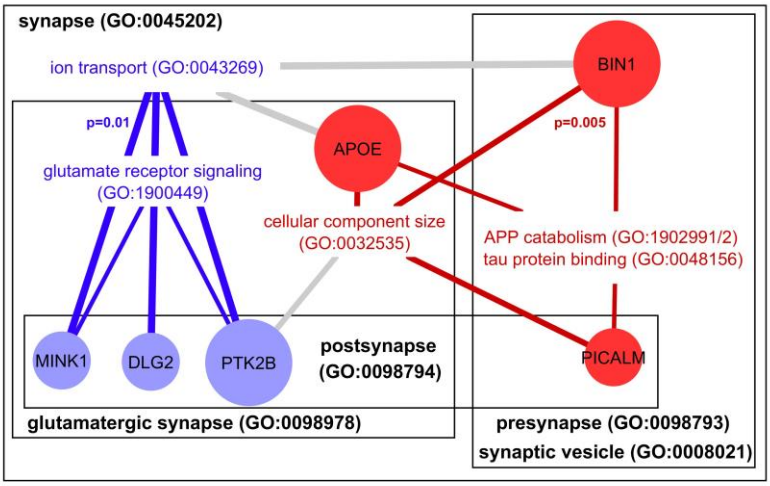

Figure 3. Enriched gene ontologies associated with proteins encoded by Synaptic PRS loci. Lines connect the Synaptic PRS loci (circular nodes) to the shared enriched biological processes and molecular functions to which they are annotated (all 25 to 100-fold enriched, all FDR adjusted p-value <0.003). Node size and line thickness reflect the number of shared nodes. Rectangular boxes group the nodes according to shared enriched cellular components, which are labeled in bold (all 21 to 62-fold enriched, all FDR adjusted p-value <0.01). The two highly inter-related clusters and associated p-values from cluster analysis are marked in blue (cluster 1) and red (cluster 2).

8. Supplementary Material

Table S1. Synapse Gene Set. Uniprot ID and names of proteins identified in (Lleo, et al., 2019) as components of the synaptic proteome are given. The associated genes retrieved from the GRCh37/hg19 reference assembly are identified by chromosome (CHR), co-ordinate (FROM TO), EntrezGene ID and Gene names (primary and synonyms).

Table S2. Synapse SNP set. The rs numbers for SNPs that lie within the Synapse Genes and that were present on the Neurochip dataset and included in the IGAP GWAS (Lambert, et al., 2013) are identified by chromosome (CHR), rs number (SNP) and base pair location (BP). The p-value for association of each SNP with LOAD in the IGAP dataset is also provided.