

## 1 **Description of Additional Supplementary Data**

### 2 **Supplementary Data 1. Supplementary Data 1 Sample Breakdown.xlsx**

3 Description of the AMP-AD MSBB population and samples measured.  
4 The first sheet contains descriptions and hyperlinks to all sheets in the Table. Sheet 2:  
5 all\_brain\_regions: Description of the entire AMP-AD MSBB population and samples measured.  
6 Samples are broken down by AD traits, and the following description of groups are present: Sex,  
7 mean age (std), APOE genotype, mean post mortem interval (std), number of samples with  
8 proteomics, number of samples with WES, number of samples with RNA-seq per brain region,  
9 mean RIN per brain region (std) and mean exonic mapping rate per brain region (std). Sheet 3:  
10 BM10 only: Description of the BM10 (discovery) dataset. Samples are broken down by AD  
11 traits, and the following description of groups are present: Sex, mean age (std), number of  
12 samples with RNA-seq, number of samples with proteomics and number of samples with WES.

### 13 **Supplementary Data 2. Supplementary Data 2 Differential Expression.xlsx**

14 Gene and Protein DE and pathway enrichments for each AD feature as defined in Supplementary  
15 Table 2. Pathway enrichments are present only if at least 1 pathway was significantly enriched  
16 for corresponding DE genes. Columns are defined in the sheets. The first sheet contains  
17 descriptions and hyperlinks to all sheets in the Table.

18 The gene DE results per trait are in the following sheets: geneDE\_Path.Dx, geneDE\_CDR,  
19 geneDE\_PlaqueMean, geneDE\_NP.1, geneDE\_CERJ, geneDE\_bbbscore,  
20 geneDE\_Path.Dx\_defvsctl, geneDE\_CDR\_geneDEfsctl, geneDE\_PlaqueMean\_geneDEfsctl,  
21 geneDE\_NP.1\_geneDEfsctl and geneDE\_CERJ\_geneDEfsctl.

22 The protein DE results per trait are in the following sheets: protDE\_PlaqueMean ,  
23 protDE\_Path.Dx, protDE\_NP.1, protDE\_CERJ, protDE\_CDR, protDE\_bbbscore,  
24 protDE\_PlaqueMean\_protDEfsctl, protDE\_Path.Dx\_protDEfsctl, protDE\_NP.1\_protDEfsctl,  
25 protDE\_CERJ\_protDEfsctl and protDE\_CDR\_protDEfsctl.

26 The GO pathway enrichments are in the following sheets where the name of the sheet contains  
27 the differential expression for a specific AD trait: geneDE\_CDR\_GO,  
28 geneDE\_PlaqueMean\_GO, geneDE\_CERJ\_GO, geneDE\_Path.Dx\_geneDEfsctl\_GO,  
29 geneDE\_CDR\_geneDEfsctl\_GO, geneDE\_PlaqueMean\_geneDEfsctl\_GO,  
30 geneDE\_NP.1\_geneDEfsctl\_GO and geneDE\_CERJ\_geneDEfsctl\_GO,  
31 protDE\_PlaqueMean\_GO, protDE\_Path.Dx\_GO, protDE\_NP.1\_GO, protDE\_CERJ\_GO,  
32 protDE\_CDR\_GO, protDE\_bbbscore\_GO, protDE\_PlaqueMean\_protDEfsctl\_GO,  
33 protDE\_Path.Dx\_protDEfsctl\_GO, protDE\_NP.1\_protDEfsctl\_GO and  
34 protDE\_CERJ\_protDEfsctl\_GO.

35 The GSEA pathway enrichments are in the following sheets where the name of the sheet  
36 contains the differential expression for a specific AD trait: geneDE\_PlaqueMean\_GSEA,  
37 geneDE\_PlaqueMean\_geneDEfsctl\_GSEA, protDE\_PlaqueMean\_GSEA,  
38 protDE\_CDR\_GSEA, protDE\_bbbscore\_GSEA, protDE\_PlaqueMean\_protDEfsctl\_GSEA,  
39 protDE\_NP.1\_protDEfsctl\_GSEA and protDE\_CERJ\_protDEfsctl\_GSEA.

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41 **Supplementary Data 3. Supplementary Data 3 Networks.xlsx**

42 Network results: Co-expression and Bayesian networks KDA results and RF Z-score ranks for  
43 gene, protein and multiscale traits. Columns are defined in the sheets. The first sheet contains  
44 descriptions and hyperlinks to all sheets in the Table.

45 The sheets contain the following results: Gene\_coexpression is the gene co-expression network;  
46 Gene\_Coexpression\_GO is the GO annotation for each module of the gene co-expression  
47 network; Protein\_Coexpression is the protein co-expression network; Protein\_Coexpression\_GO  
48 is the GO annotation for each module of the protein co-expression network;  
49 Multiscale\_Coexpression is the multiscale co-expression network;  
50 Multiscale\_Coexp\_Breakdown is a table detailing for each module of the multiscale co-  
51 expression network the number of genes and protein it contains; Union\_DE\_genes contains the  
52 union of DE genes across all AD traits at FDR<0.05 that is projected onto the gene co-expression  
53 network; Union\_DE\_proteins contains the union of DE proteins across all AD traits at  
54 FDR<0.05 that is projected onto the protein co-expression network; signif\_modules\_gene is a  
55 table with the gene co-expression modules enriched for the union of DE genes;  
56 signif\_modules\_protein is a table with the protein co-expression modules enriched for the union  
57 of DE proteins; Seeding\_gene\_list\_before\_PEXA is the expanded AD DE signature containing  
58 all DE genes and all genes in gene co-expression modules enriched for DE genes;  
59 Seeding\_gene\_list\_after\_PEXA is the seeding gene list from which the BN are constructed,  
60 containing all DE genes and all genes in gene co-expression modules enriched for DE genes as  
61 well as genes added from protein-protein interaction networks and KEGG pathways; Gene\_BN  
62 is the gene only BN; Protein\_BN is the protein only BN and Multiscale\_BN is the multiscale  
63 BN. KDA\_Gene\_BN\_ordered is the results of local KDA for all AD traits gene DE lists and  
64 gene co-expression modules in the gene BN ordered by their information Z-score rank;  
65 KDA\_Protein\_BN\_ordered is the results of local KDA for all AD traits protein DE lists and  
66 protein co-expression modules in the protein BN ordered by their information Z-score rank;  
67 KDA\_Multiscale\_BN\_ordered is the results of local KDA for all AD traits gene and protein DE  
68 lists and gene and protein co-expression modules in the multiscale BN ordered by their  
69 information Z-score rank; KDA\_Gene\_BN\_DE\_ordered is the results of local KDA for all AD  
70 traits gene DE lists in the gene BN ordered by their information Z-score rank;  
71 KDA\_Protein\_BN\_DE\_ordered is the results of local KDA for all AD traits protein DE lists in  
72 the protein BN ordered by their information Z-score rank; KDA\_Multiscale\_BN\_DE\_ordered is  
73 the results of local KDA for all AD traits gene and protein DE lists in the multiscale BN ordered  
74 by their information Z-score rank; Gene\_BN\_global\_KDs is a list of the global KDs for the gene  
75 BN; Protein\_BN\_global\_KDs is a list of the global KDs for the protein BN;  
76 Multiscale\_BN\_global\_KDs is a list of the global KDs for the multiscale BN. Gene\_RF\_rank is  
77 the ranks from the weighted z-score random forest classifiers for every gene in the gene  
78 expression data; Protein\_RF\_rank is the ranks from the weighted z-score random forest  
79 classifiers for every protein in the protein expression data; Multiscale\_RF\_rank is the ranks from  
80 the weighted z-score random forest classifiers for every gene and protein in the gene and protein  
81 expression data.

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83 **Supplementary Data 4. Supplementary Data 4 QTLs.xlsx**

84 QTL results: eQTL, pQTL and CIT results. Columns are defined in the sheets. The first sheet  
85 contains descriptions and hyperlinks to all sheets in the Table.

86 The sheets contain the following results: eGenes is a table of eGene results with each line being a  
87 gene and its most significant eQTL; eProteins is a table of eProtein results with each line being a  
88 protein and its most significant pQTL; common\_e\_p\_QTL is a table defining the e- and p-QTL  
89 under shared SNP control; eGenes\_forNetwork is a table containing the eGenes that were  
90 included in the BNs; eProteins\_forNetwork is a table containing the eProteins that were included  
91 in the BNs; CIT\_gene\_to\_protein is a table with the results of the CIT test for genes and proteins  
92 under shared SNP control for the gene parent model; CIT\_protein\_to\_gene is a table with the  
93 results of the CIT test for genes and proteins under shared SNP control for the protein parent  
94 model (reactive model).

#### 95 **Supplementary Data 5. Supplementary Data 5 Replication.xlsx**

96 Replication results in BM22, BM44, BM36 and ROSMAP. Columns are defined in the sheets.  
97 The first sheet contains descriptions and hyperlinks to all sheets in the Table.

98 The DE results per trait are in the following sheets (only genes with FDR<0.05 are shown):

99 BM22\_DE\_bbscore, BM22\_DE\_CDR, BM22\_DE\_CDR\_defvsctl, BM22\_DE\_CERJ,  
100 BM22\_DE\_CERJ\_defvsctl, BM22\_DE\_NP.1, BM22\_DE\_NP.1\_defvsctl,  
101 BM22\_DE\_PATH.Dx, BM22\_DE\_PATH\_Dx\_defvsctl, BM22\_DE\_PlaqueMean,  
102 BM22\_DE\_PlaqueMean\_defvsctl, BM44\_DE\_bbscore, BM44\_DE\_CDR,  
103 BM44\_DE\_CDR\_defvsctl, BM44\_DE\_CERJ, BM44\_DE\_CERJ\_defvsctl, BM44\_DE\_NP.1,  
104 BM44\_DE\_NP.1\_defvsctl, BM44\_DE\_PATH.Dx, BM44\_DE\_PATH\_Dx\_defvsctl,  
105 BM44\_DE\_PlaqueMean, BM44\_DE\_PlaqueMean\_defvsctl, BM36\_DE\_bbscore,  
106 BM36\_DE\_CDR, BM36\_DE\_CDR\_defvsctl, BM36\_DE\_CERJ, BM36\_DE\_CERJ\_defvsctl,  
107 BM36\_DE\_NP.1, BM36\_DE\_NP.1\_defvsctl, BM36\_DE\_PATH.Dx,  
108 BM36\_DE\_PATH\_Dx\_defvsctl, BM36\_DE\_PlaqueMean, BM36\_DE\_PlaqueMean\_defvsctl,  
109 ROSMAP\_DE\_braaksc, ROSMAP\_DE\_ceradsc\_defvsctl, ROSMAP\_DE\_ceradsc,  
110 ROSMAP\_DE\_cogdx\_defvsctl, ROSMAP\_DE\_cogdx.

111 The GO pathway enrichments are in the following sheets where the name of the sheet contains  
112 the differential expression for a specific AD trait (only terms with FDR<0.05 are shown):

113 BM22\_DE\_CERJ\_GO, BM22\_DE\_NP.1\_defvsctl\_GO, BM22\_DE\_PlaqueMean\_GO,  
114 BM22\_DE\_PlaqueMean\_defvsctl\_GO, BM36\_DE\_bbscore\_GO, BM36\_DE\_CDR\_GO,  
115 BM36\_DE\_CDR\_defvsctl\_GO, BM36\_DE\_CERJ\_GO, BM36\_DE\_CERJ\_defvsctl\_GO,  
116 BM36\_DE\_NP.1\_GO, BM36\_DE\_NP.1\_defvsctl\_GO, BM36\_DE\_PATH.Dx\_GO,  
117 BM36\_DE\_PATH\_Dx\_defvsctl\_GO, BM36\_DE\_PlaqueMean\_GO,  
118 BM36\_DE\_PlaqueMean\_defvsctl\_GO, ROSMAP\_DE\_braaksc\_GO,  
119 ROSMAP\_DE\_ceradsc\_defvsctl\_GO, ROSMAP\_DE\_ceradsc\_GO,  
120 ROSMAP\_DE\_cogdx\_defvsctl\_GO, ROSMAP\_DE\_cogdx\_GO. There was no GO pathway  
121 enrichments for BM44.

122 The remaining sheets contain the following results: BM22\_Union\_DE\_genes contains the union  
123 of DE genes across all AD traits at FDR<0.05 that is projected onto the gene co-expression  
124 network; BM22\_Gene\_coexpression is the gene co-expression network;  
125 BM22\_Gene\_Coexpression\_GO is the GO annotation for each module of the gene co-expression  
126 network; BM22\_signif\_modules\_gene is a table with the gene co-expression modules enriched  
127 for the union of DE genes; BM22\_eGenes is a table of eGene results with each line being a gene  
128 and its most significant eQTL; BM22\_eGenes\_forNetwork is a table containing the eGenes that  
129 were included in the BNs; BM22\_Seeding\_gene\_list is the expanded AD DE signature  
130 containing all DE genes and all genes in gene co-expression modules enriched for DE genes;

131 BM22\_Gene\_BN is the gene only BN; BM22\_local\_KDA is the results of local KDA for all AD  
132 traits gene DE lists and gene co-expression modules in the gene BN; BM22\_global\_KDA is a list  
133 of the global KDs for the gene BN; BM44\_Union\_DE\_genes contains the union of DE genes  
134 across all AD traits at FDR<0.05 that is projected onto the gene co-expression network;  
135 BM44\_topCorGenes is a table of all the union DE genes and the union of their top 10 genes most  
136 correlated genes as defined in the methods (Seeding gene list construction);  
137 BM44\_Gene\_coexpression is the gene co-expression network; BM44\_Gene\_Coexpression\_GO  
138 is the GO annotation for each module of the gene co-expression network;  
139 BM44\_signif\_modules\_gene is a table with the gene co-expression modules enriched for the  
140 union of DE genes and their top 10 correlated genes; BM44\_eGenes is a table of eGene results  
141 with each line being a gene and its most significant eQTL; BM44\_eGenes\_forNetwork is a table  
142 containing the eGenes that were included in the BNs; BM44\_Seeding\_gene\_list is the expanded  
143 AD DE signature containing all DE genes and all genes in gene co-expression modules enriched  
144 for DE genes; BM44\_Gene\_BN is the gene only BN; BM44\_local\_KDA is the results of local  
145 KDA for all AD traits gene DE lists and gene co-expression modules in the gene BN;  
146 BM44\_global\_KDA is a list of the global KDs for the gene BN; BM36\_Union\_DE\_genes  
147 contains the union of DE genes across all AD traits at FDR<0.05 that is projected onto the gene  
148 co-expression network; BM36\_Gene\_coexpression is the gene co-expression network;  
149 BM36\_Gene\_Coexpression\_GO is the GO annotation for each module of the gene co-expression  
150 network; BM36\_signif\_modules\_gene is a table with the gene co-expression modules enriched  
151 for the union of DE genes; BM36\_eGenes is a table of eGene results with each line being a gene  
152 and its most significant eQTL; BM36\_eGenes\_forNetwork is a table containing the eGenes that  
153 were included in the BNs; BM36\_Seeding\_gene\_list is the expanded AD DE signature  
154 containing all DE genes and all genes in gene co-expression modules enriched for DE genes;  
155 BM36\_Gene\_BN is the gene only BN; BM36\_local\_KDA is the results of local KDA for all AD  
156 traits gene DE lists and gene co-expression modules in the gene BN; BM36\_global\_KDA is a list  
157 of the global KDs for the gene BN; ROSMAP\_Union\_DE\_genes contains the union of DE genes  
158 across all AD traits at FDR<0.05 that is projected onto the gene co-expression network;  
159 ROSMAP\_Gene\_coexpression is the gene co-expression network;  
160 ROSMAP\_Gene\_Coexpression\_GO is the GO annotation for each module of the gene co-  
161 expression network; ROSMAP\_signif\_modules\_gene is a table with the gene co-expression  
162 modules enriched for the union of DE genes; ROSMAP\_eGenes is a table of eGene results with  
163 each line being a gene and its most significant eQTL; ROSMAP\_eGenes\_forNetwork is a table  
164 containing the eGenes that were included in the BNs; ROSMAP\_Seeding\_gene\_list is the  
165 expanded AD DE signature containing all DE genes and all genes in gene co-expression modules  
166 enriched for DE genes; ROSMAP\_Gene\_BN is the gene only BN; ROSMAP\_local\_KDA is the  
167 results of local KDA for all AD traits gene DE lists and gene co-expression modules in the gene  
168 BN; ROSMAP\_global\_KDA is a list of the global KDs for the gene BN.

#### 169 **Supplementary Data 6. Supplementary Data 6 Mouse Differential Expression.xlsx**

170 Results of the mouse DE for both molecular validation models (genes with FDR<0.05 are  
171 indicated in bold). Columns are defined in the sheets. The first sheet contains descriptions and  
172 hyperlinks to all sheets in the Table.  
173 The sheets contain the following results: FADAAVGFP.FADAAVVGFP is the results if the DE  
174 between 5xFAD,AAV-VGF and 5xFAD,AAV-GFP (genes with FDR<0.05 are indicated in

175 bold); FADVGFhom.FADVGFwt is the results of the DE between 5xFAD, VGF<sup>Δ/Δ</sup> and 5xFAD  
176 with normal levels of VGF (genes with FDR<0.05 are indicated in bold).  
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