

A genome-wide association meta-analysis of all-cause and vascular dementia

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- 197 Nuffield Department of Clinical Neurosciences, Oxford University
- 198 University of Oxford, Oxford UK
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- 214 Department of Clinical Biochemistry, Copenhagen University Hospital – Rigshospitalet, Copenhagen Denmark & Department of Clinical Medicine, Copenhagen Denmark.
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Supplementary Figures

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Introduction

1 - Cross-ancestry meta-analysis: ancestry PCs plot

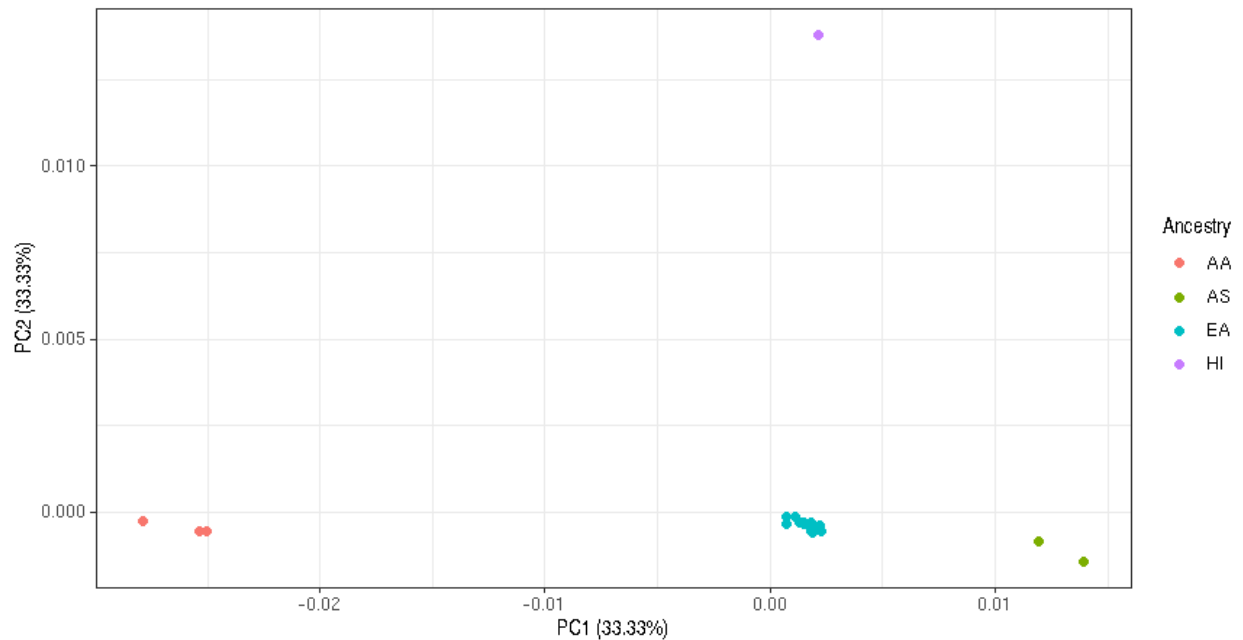


Figure S1: Principal components generated using the mean allele frequency difference between studies. Principal components (PCs) are generated using MR-MEGA from a matrix of mean pairwise allele frequency differences between cohorts (total $n=$). Color denotes self-reported ancestry for each cohort. Selected outliers are labeled with cohort names. Three PCs were chosen as per the author's recommendations and, as shown, are sufficient to separate self-reported ancestry groups.

2 – Variant plots

2 – 1 All-cause dementia genome-wide significant variants

2 – 1 – 1 APOE locus

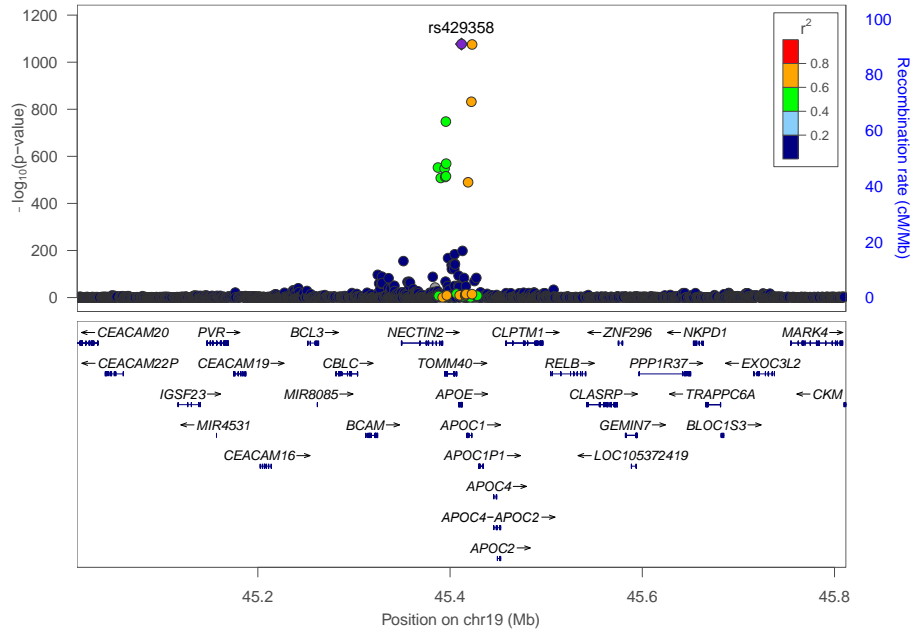


Figure S2: Regional association plot showing the genomic region containing APOE. For each SNP, the P-value (log10 scale) of the association with ACD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

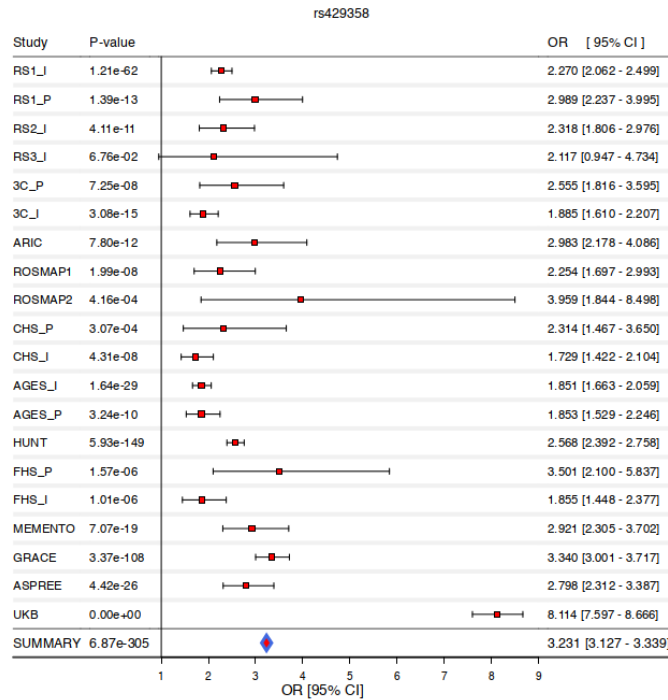


Figure S3: Forest plot of the locus near APOE in ACD GWAS of European ancestry.

2 – 1 – 2 BIN1 locus

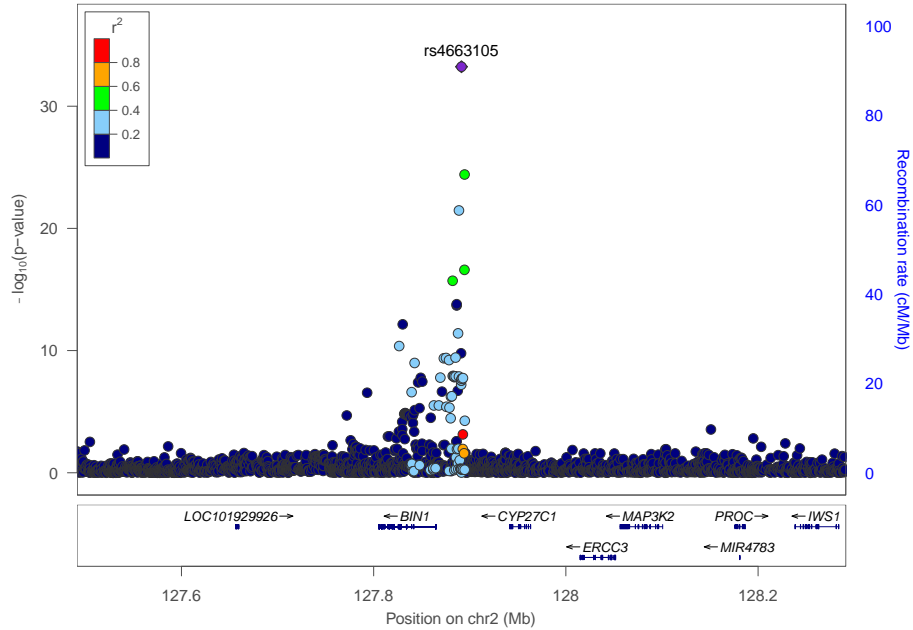


Figure S4: Regional association plot showing the genomic region containing **BIN1**. For each SNP, the P-value (log10 scale) of the association with ACD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

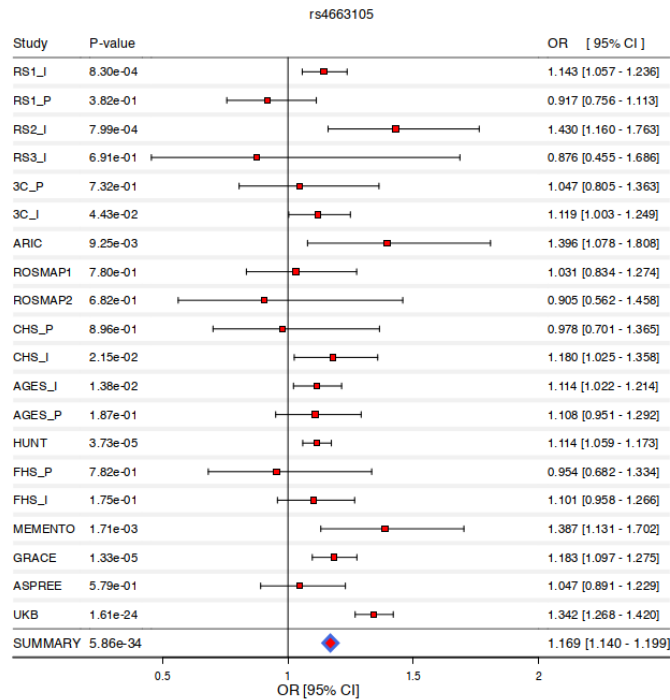


Figure S5: Forest plot of the locus near **BIN1** in ACD GWAS of European ancestry.

2 – 1 – 3 MS4A6A locus

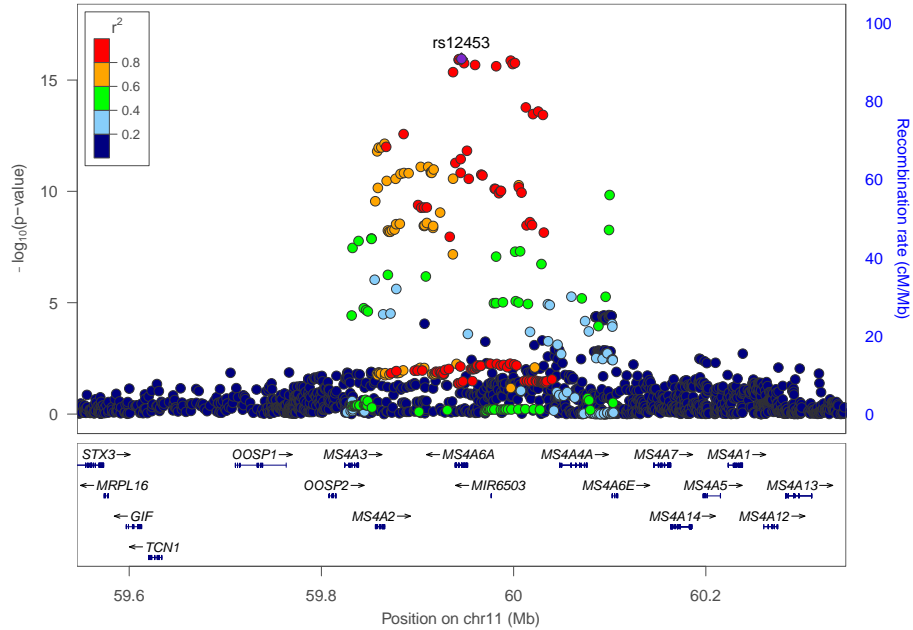


Figure S6: Regional association plot showing the genomic region containing MS4A6A. For each SNP, the P-value (log10 scale) of the association with ACD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

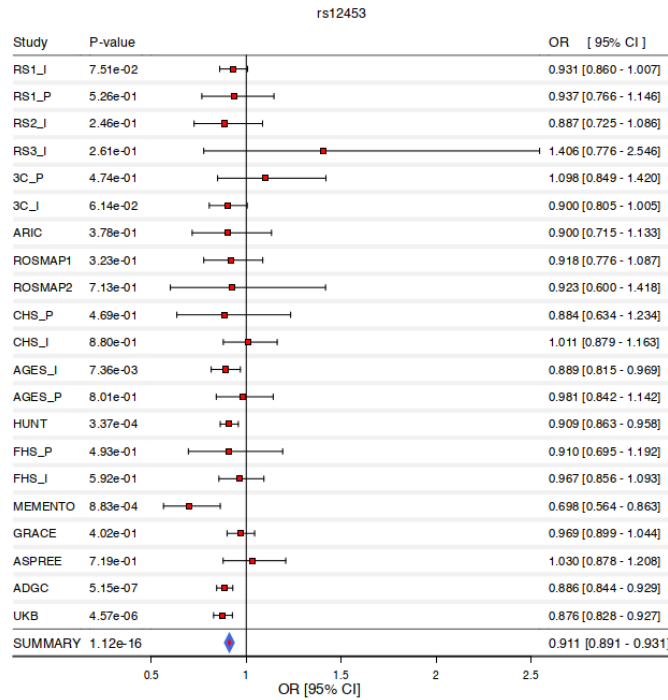


Figure S7: Forest plot of the locus near MS4A6A in ACD GWAS of European ancestry.

2 – 1 – 4 PICALM locus

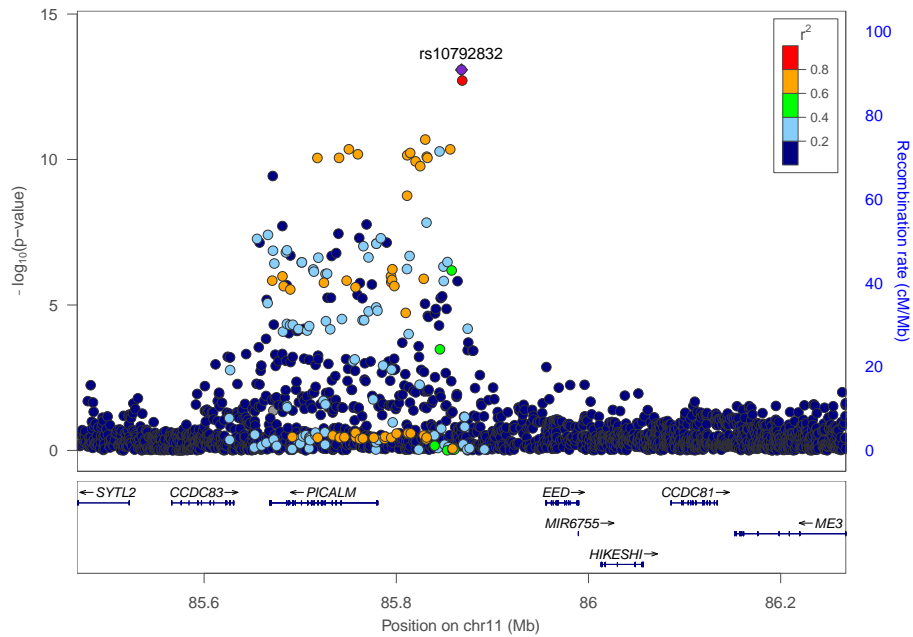


Figure S8: Regional association plot showing the genomic region containing **PICALM**. For each SNP, the P-value (log10 scale) of the association with ACD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

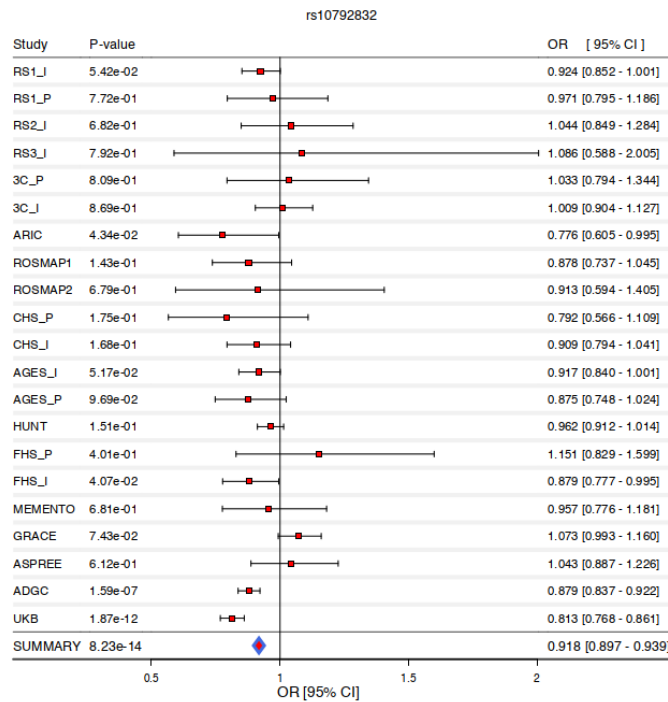


Figure S9: Forest plot of the locus near **PICALM** in ACD GWAS of European ancestry.

2 – 1 – 5 CD2AP locus

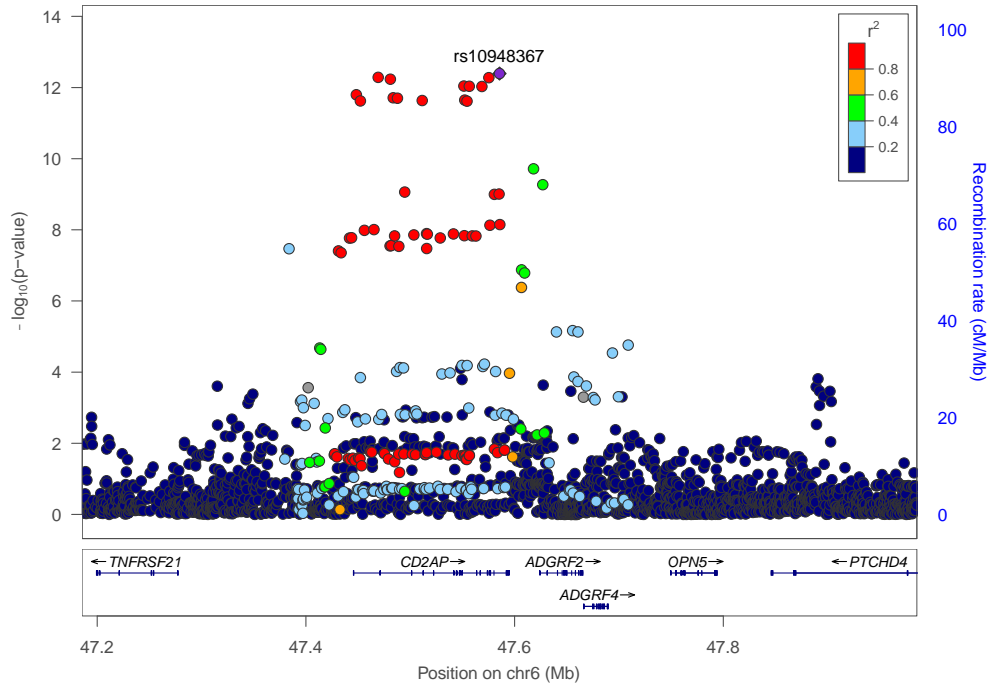


Figure S10: Regional association plot showing the genomic region containing CD2AP. For each SNP, the P-value (log10 scale) of the association with ACD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

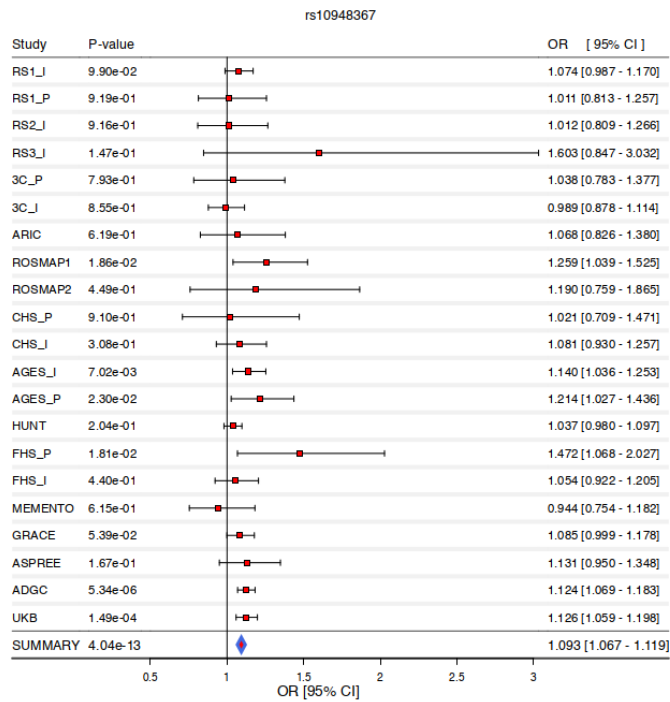


Figure S11: Forest plot of the locus near CD2AP in ACD GWAS of European ancestry.

2 – 1 – 6 ACE locus

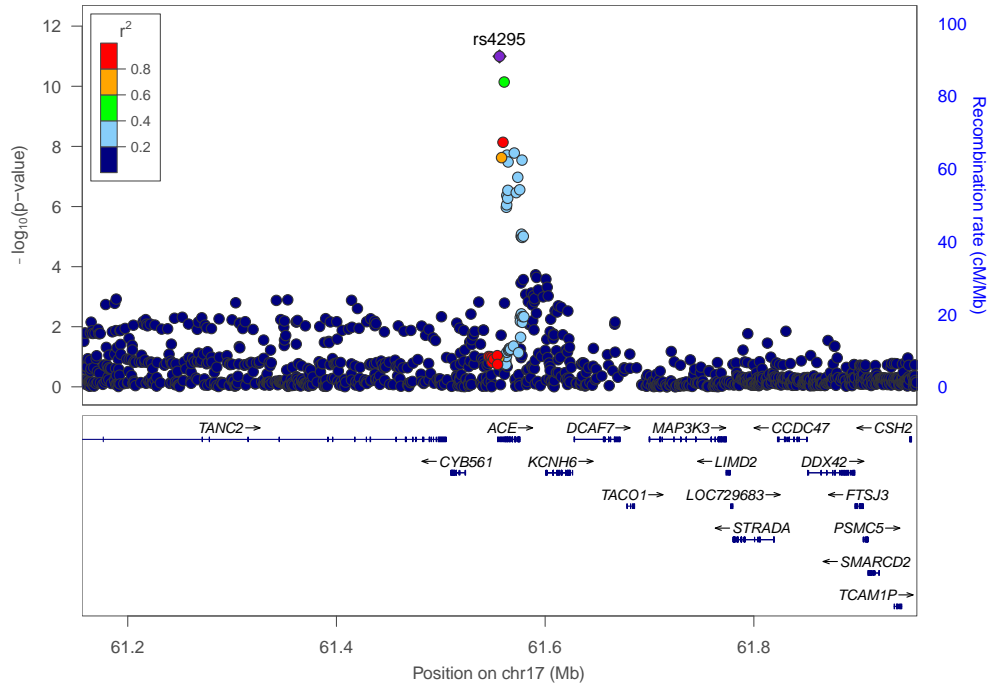


Figure S12: Regional association plot showing the genomic region containing ACE. For each SNP, the P-value (log10 scale) of the association with ACD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

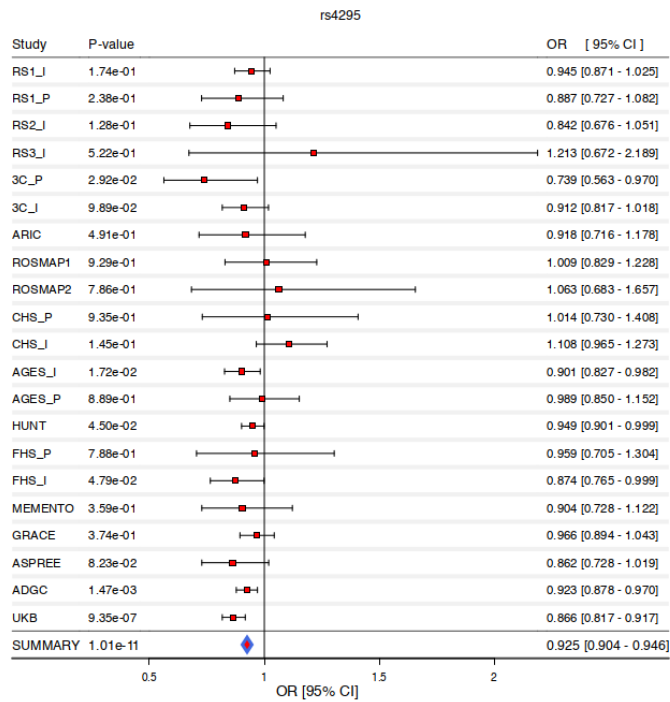


Figure S13: Forest plot of the locus near ACE in ACD GWAS of European ancestry.

2 – 1 – 7 CR1 locus

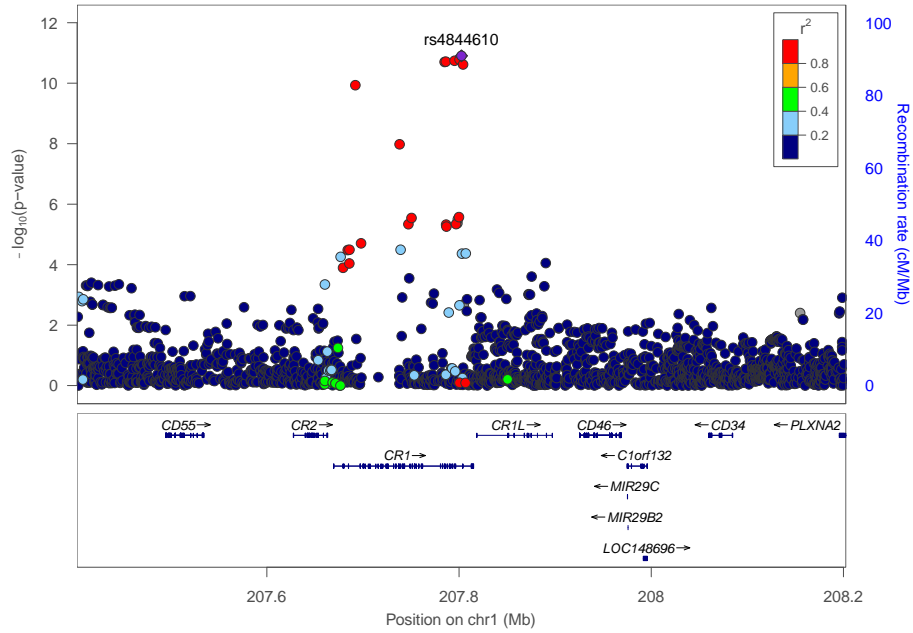


Figure S14: Regional association plot showing the genomic region containing CR1. For each SNP, the P-value (log10 scale) of the association with ACD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

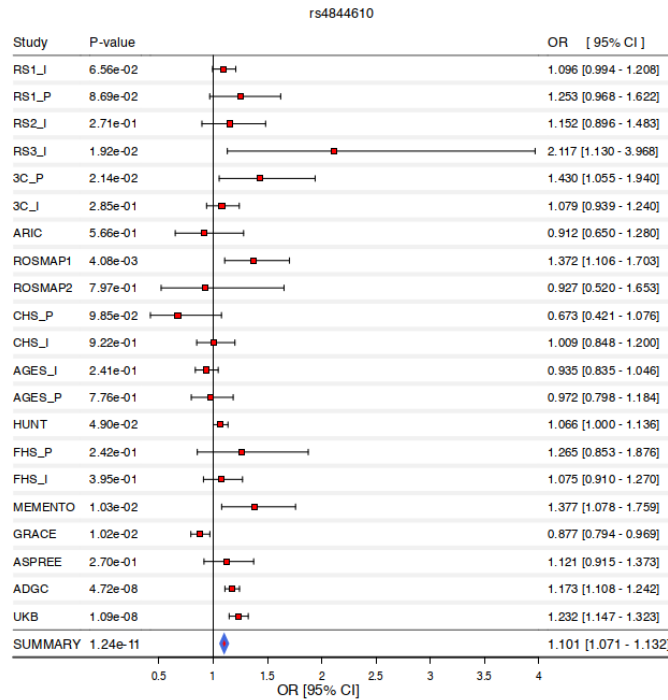


Figure S15: Forest plot of the locus near CR1 in ACD GWAS of European ancestry.

2 – 1 – 8 PILRB locus

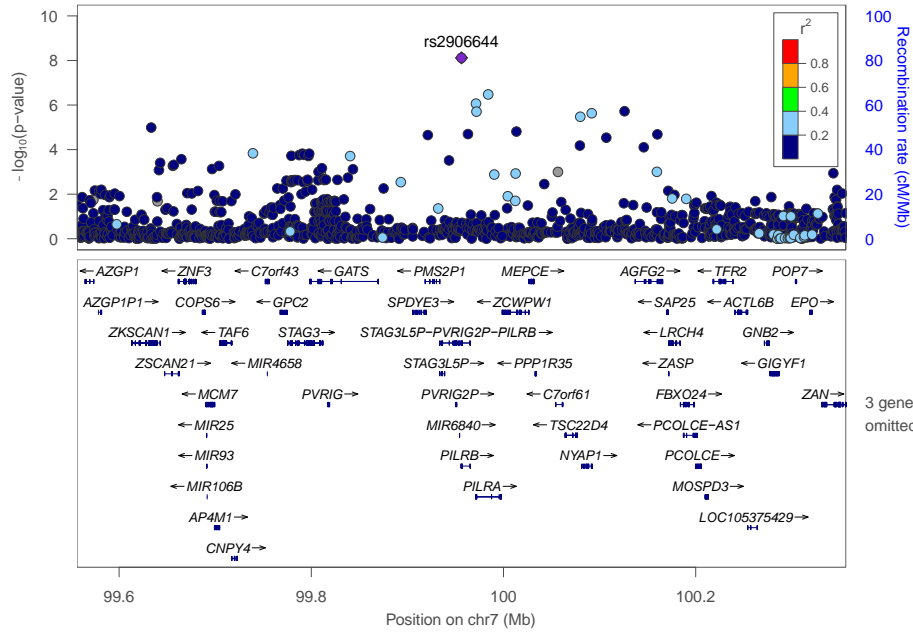


Figure S16: Regional association plot showing the genomic region containing **PILRB**. For each SNP, the P-value (log10 scale) of the association with ACD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

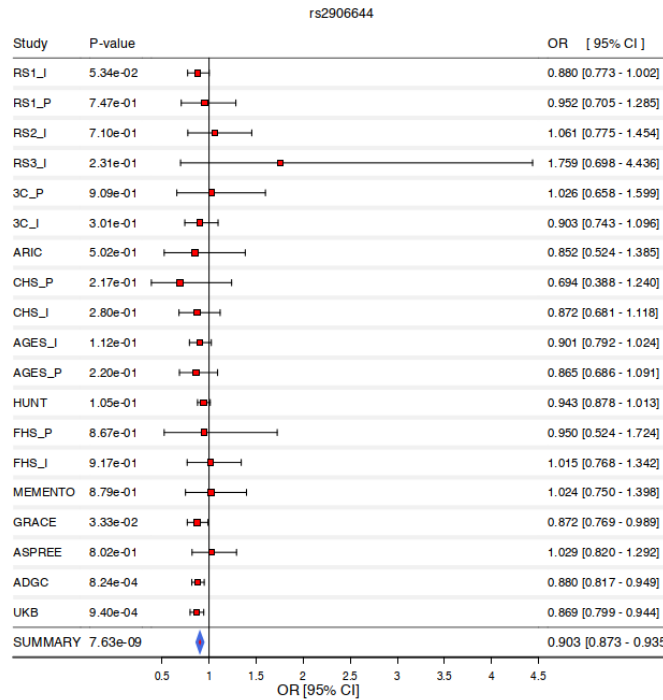


Figure S17: Forest plot of the locus near **PILRB** in ACD GWAS of European ancestry.

2 – 1 – 9 ABCA7 locus

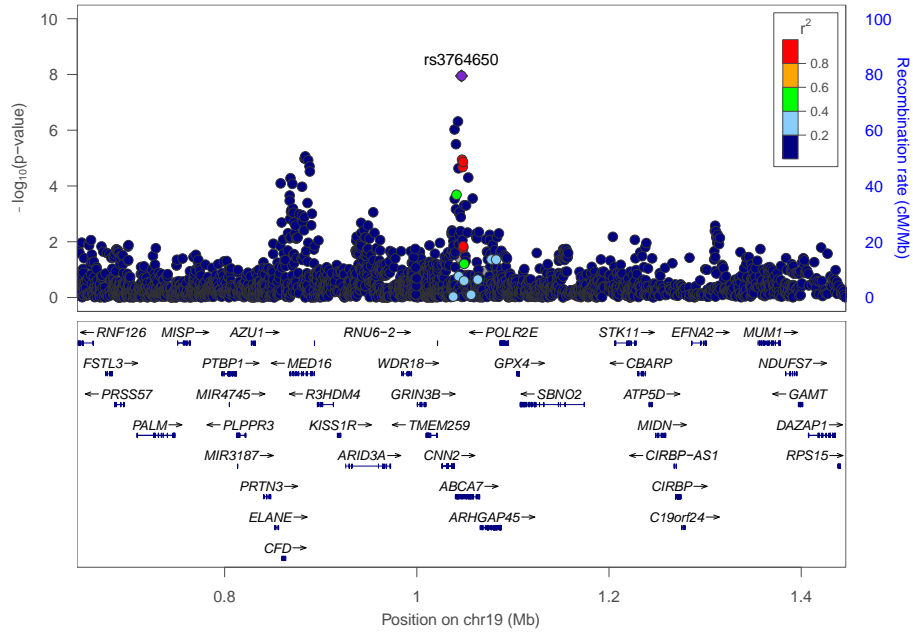


Figure S18: Regional association plot showing the genomic region containing ABCA7. For each SNP, the P-value (log10 scale) of the association with ACD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

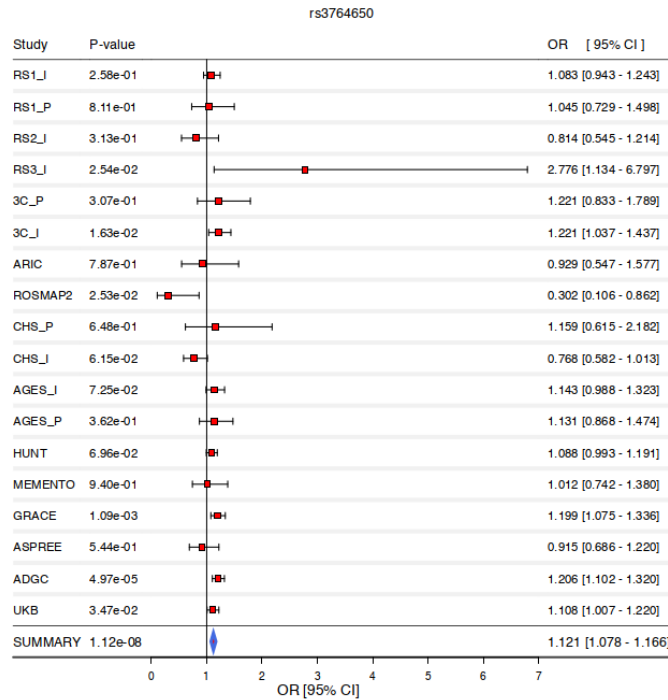


Figure S19: Forest plot of the locus near ABCA7 in ACD GWAS of European ancestry.

2 – 1 – 10 SLC24A4 locus

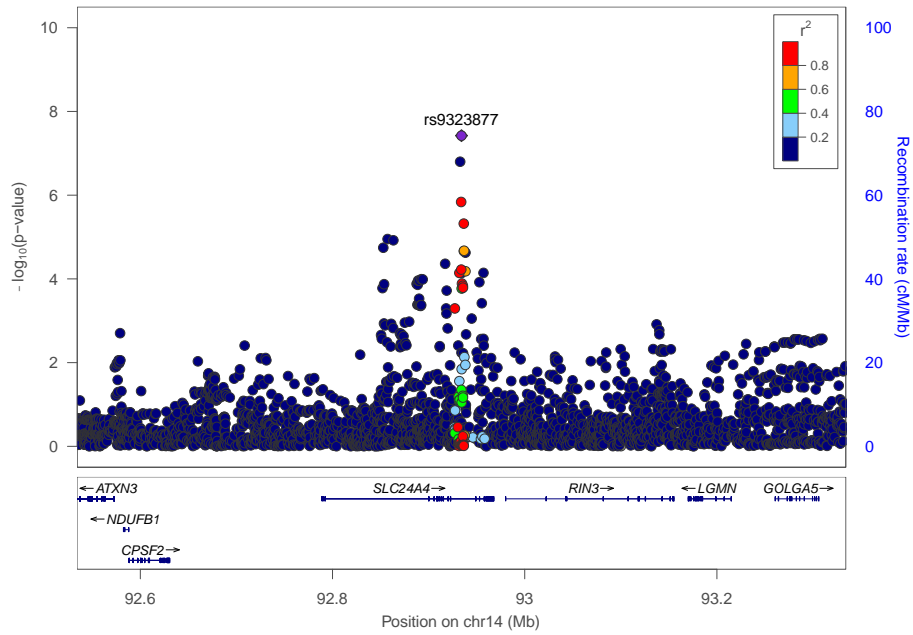


Figure S20: Regional association plot showing the genomic region containing SLC24A4. For each SNP, the P-value (log10 scale) of the association with ACD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

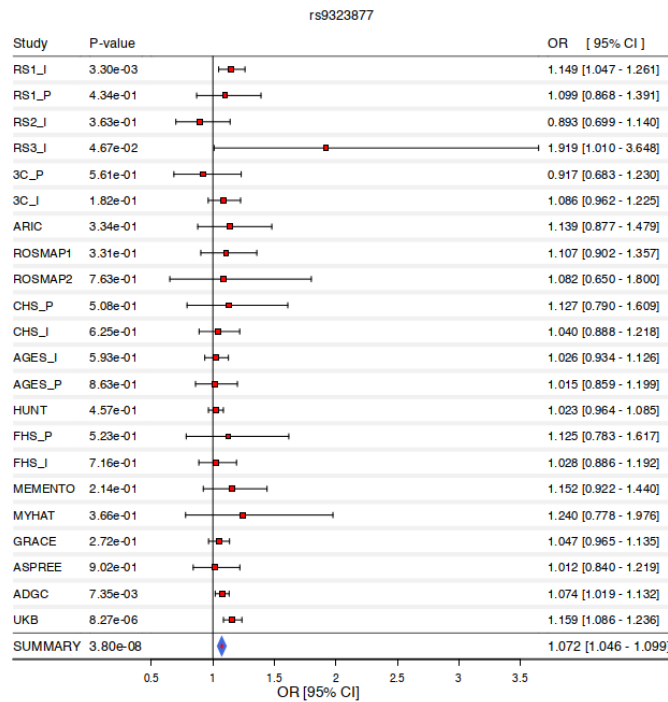


Figure S21: Forest plot of the locus near SLC24A4 in ACD GWAS of European ancestry.

2 – 2 All-cause dementia suggestive variants
 2 – 2 – 1 ANO3 locus

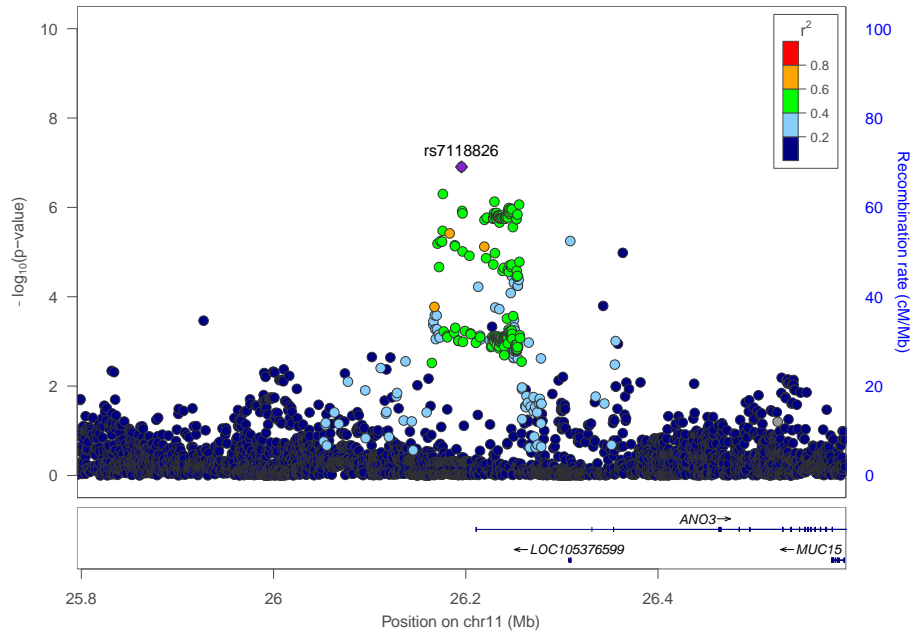


Figure S22: Regional association plot showing the genomic region containing ANO3. For each SNP, the P-value (log10 scale) of the association with ACD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

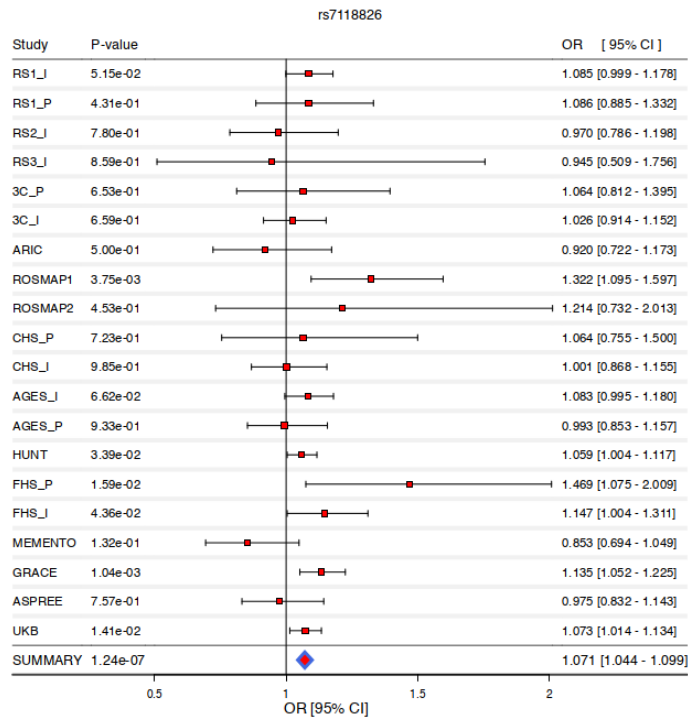


Figure S23: Forest plot of the locus near ANO3 in ACD GWAS of European ancestry.

2 – 2 – 2 SEMA4D locus

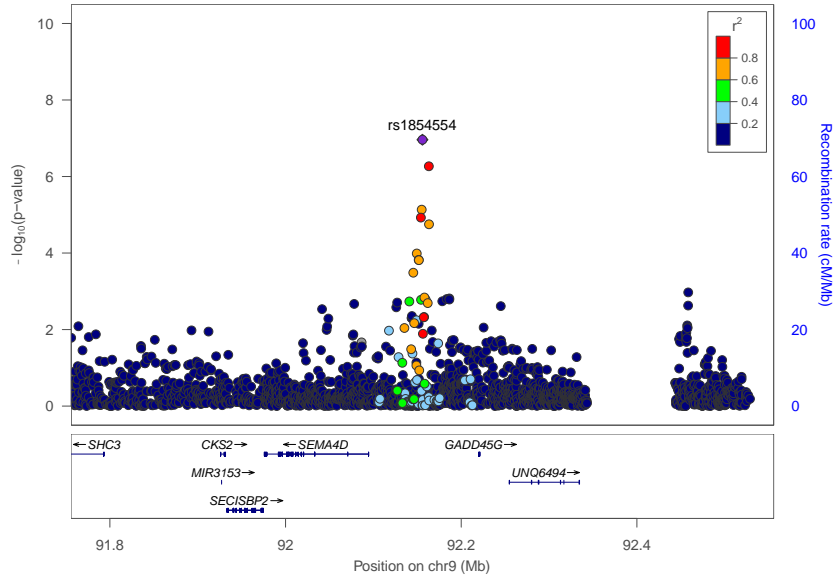


Figure S24: Regional association plot showing the genomic region containing **SEMA4D**. For each SNP, the P-value (log10 scale) of the association with ACD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

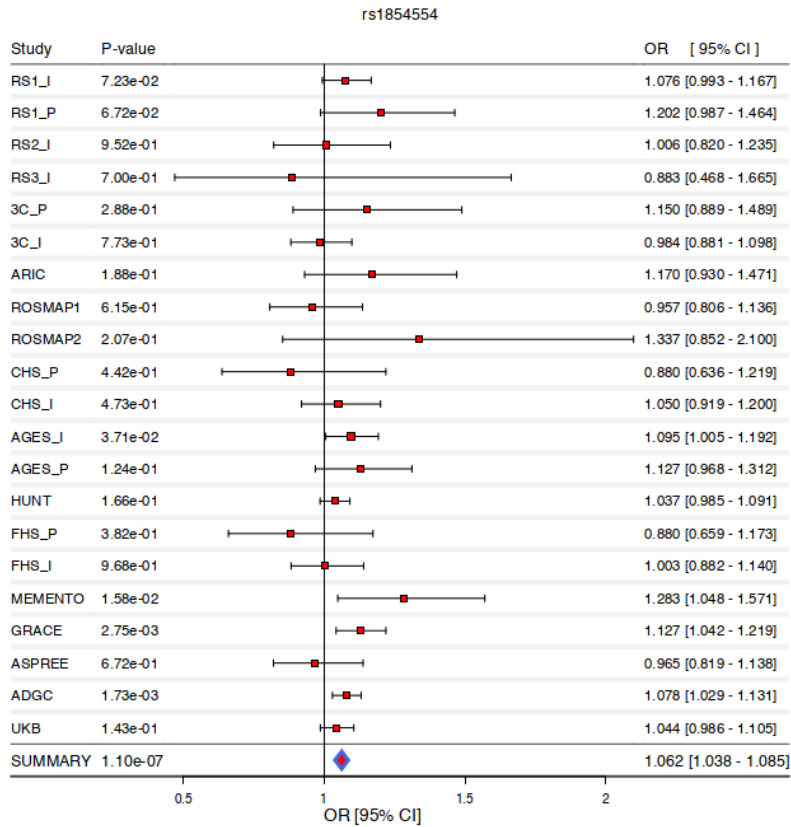


Figure S25: Forest plot of the locus near **SEMA4D** in ACD GWAS of European ancestry.

2 – 2 – 3 RBFOX1 locus

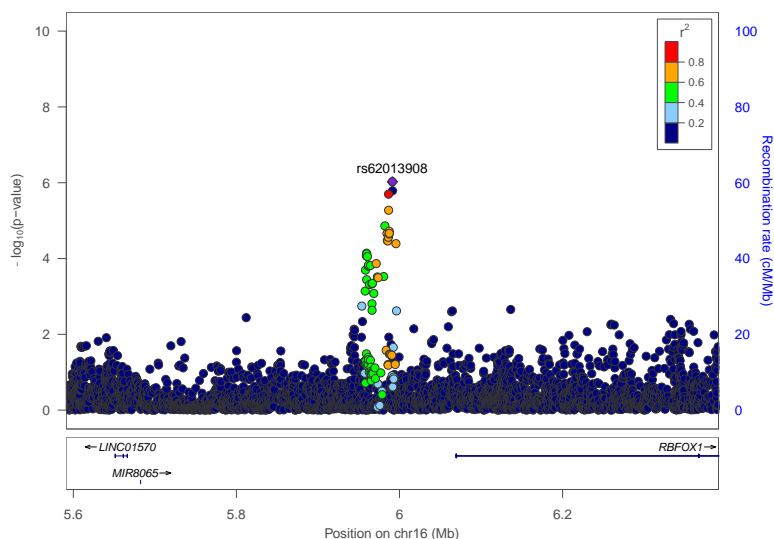


Figure S26: Regional association plot showing the genomic region containing **RBFOX1**. For each SNP, the P-value (log₁₀ scale) of the association with ACD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

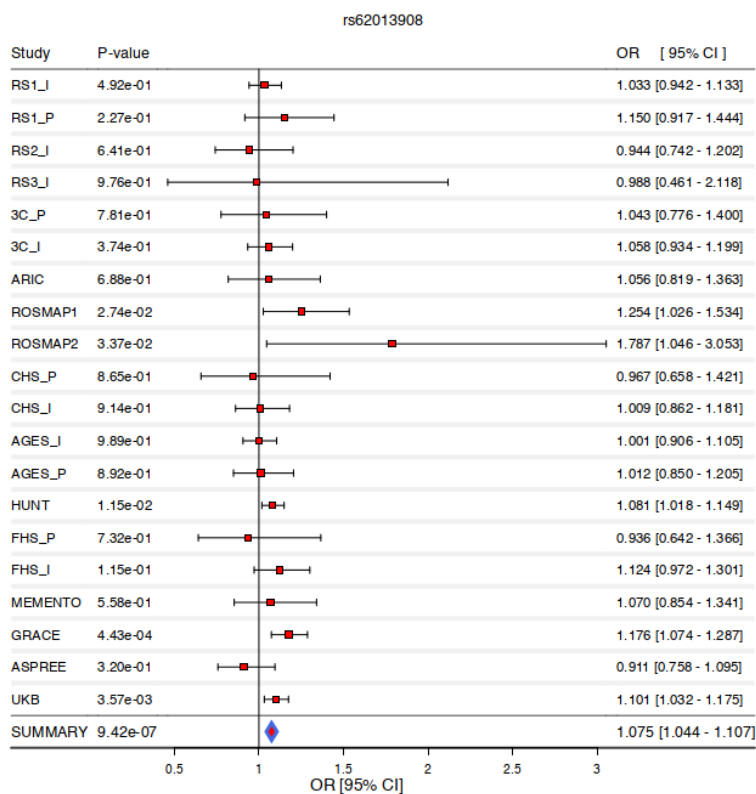


Figure S27: Forest plot of the locus near **RBFOX1** in ACD GWAS of European ancestry.

2 – 2 – 4 TRIB1 locus

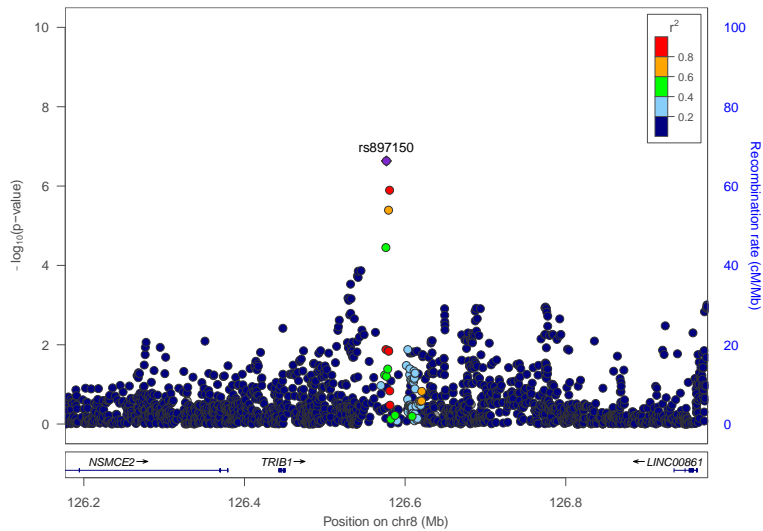


Figure S28: Regional association plot showing the genomic region containing TRIB1. For each SNP, the P-value (log10 scale) of the association with ACD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

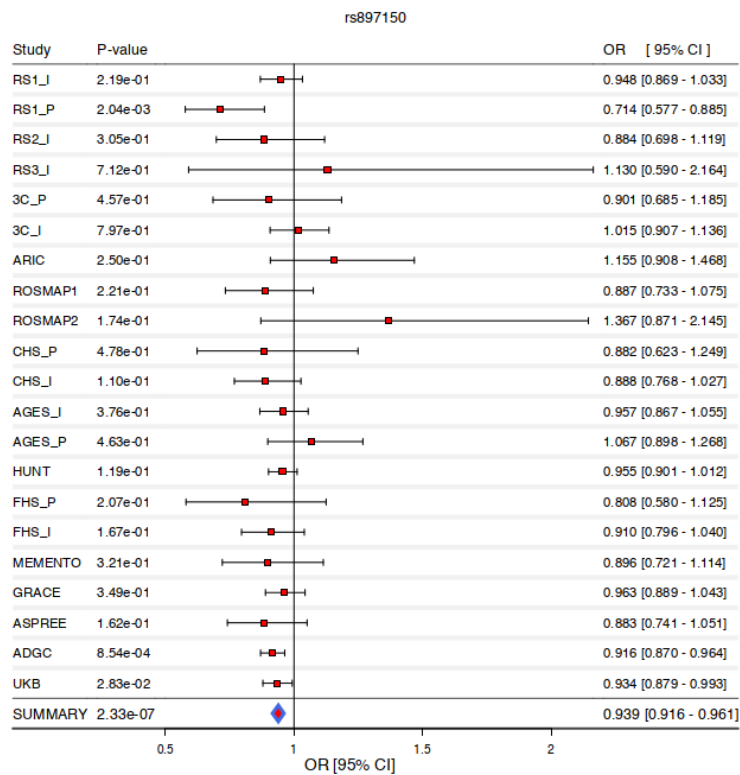


Figure S29: Forest plot of the locus near TRIB1 in ACD GWAS of European ancestry.

2 – 2 – 5 HBEGF locus

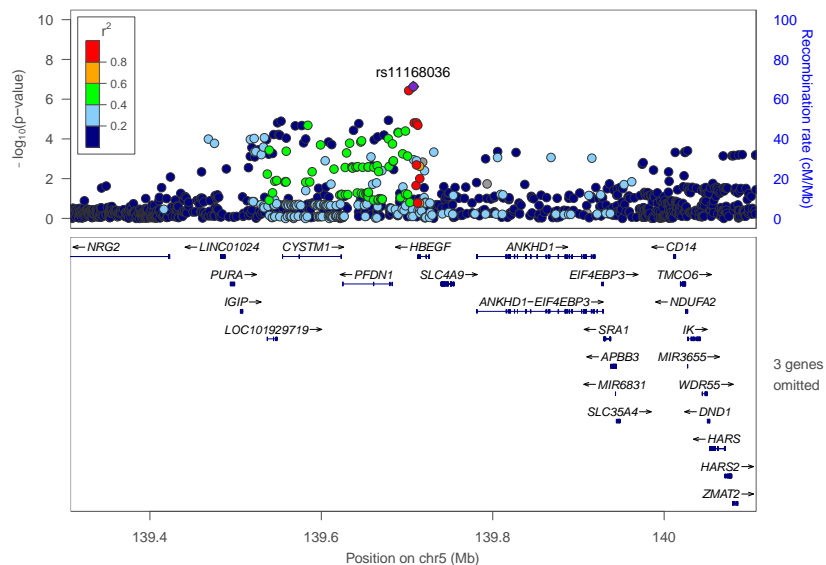


Figure S30: Regional association plot showing the genomic region containing HBEGF. For each SNP, the P-value (log10 scale) of the association with ACD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

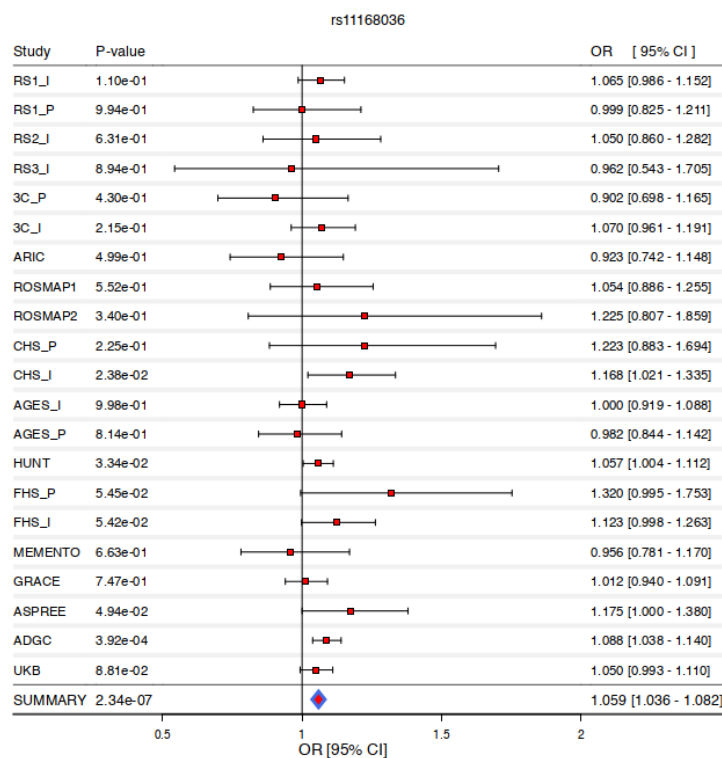


Figure S31: Forest plot of the locus near HBEGF in ACD GWAS of European ancestry.

2 – 2 – 5 ZNF652 locus

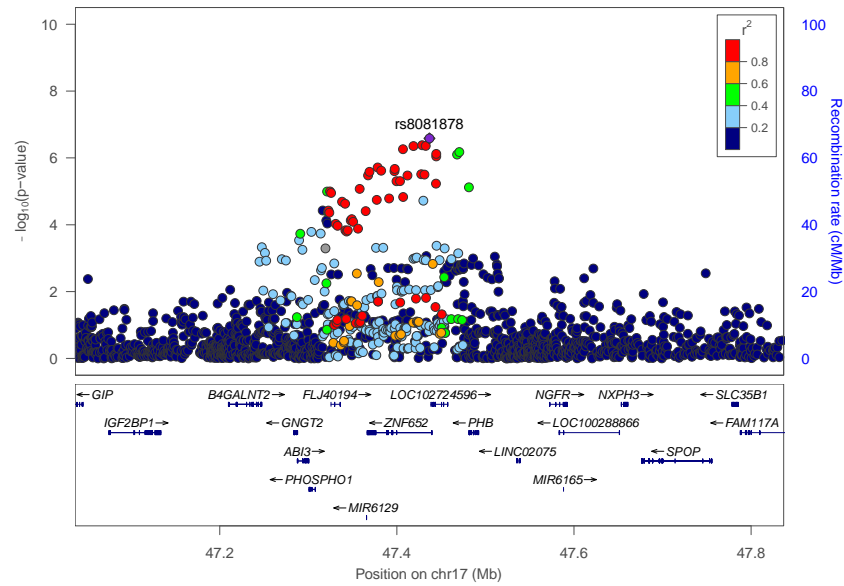


Figure S32: Regional association plot showing the genomic region containing ZNF652. For each SNP, the P-value (log10 scale) of the association with ACD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

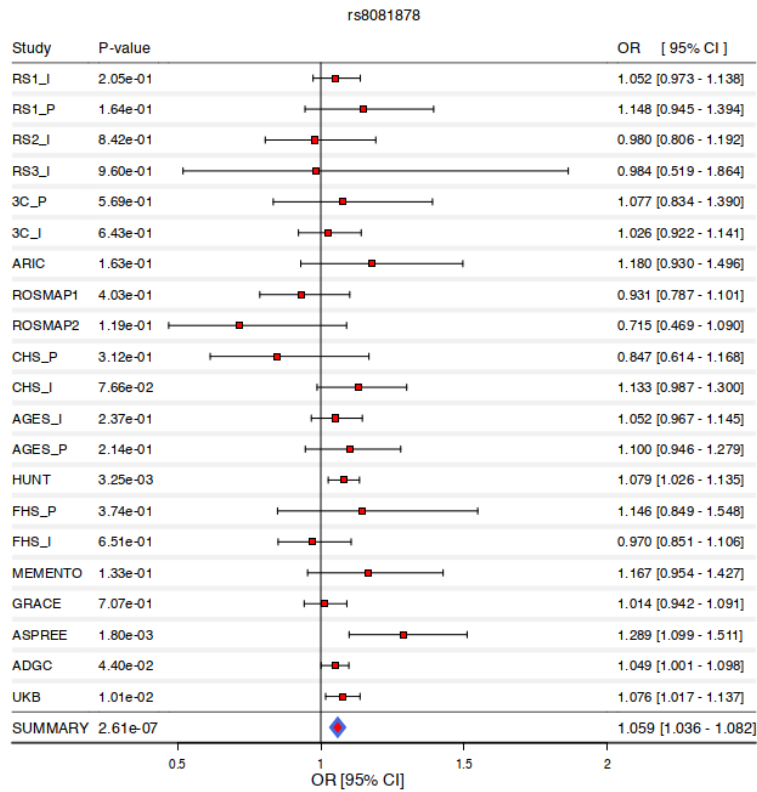


Figure S33: Forest plot of the locus near ZNF652 in ACD GWAS of European ancestry.

2 – 2 – 6 SREBF1 locus

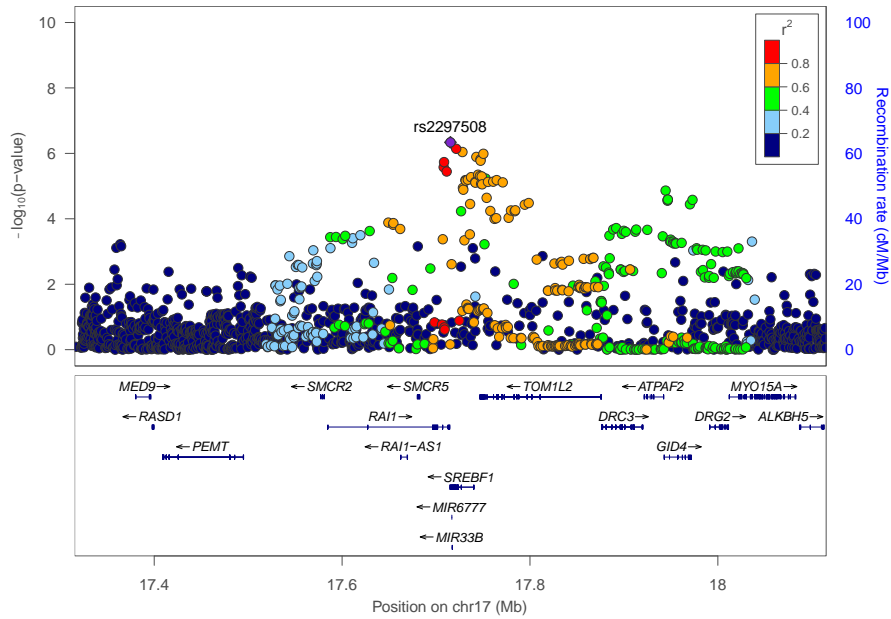


Figure S34: Regional association plot showing the genomic region containing *SREBF1*. For each SNP, the P-value (log10 scale) of the association with ACD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

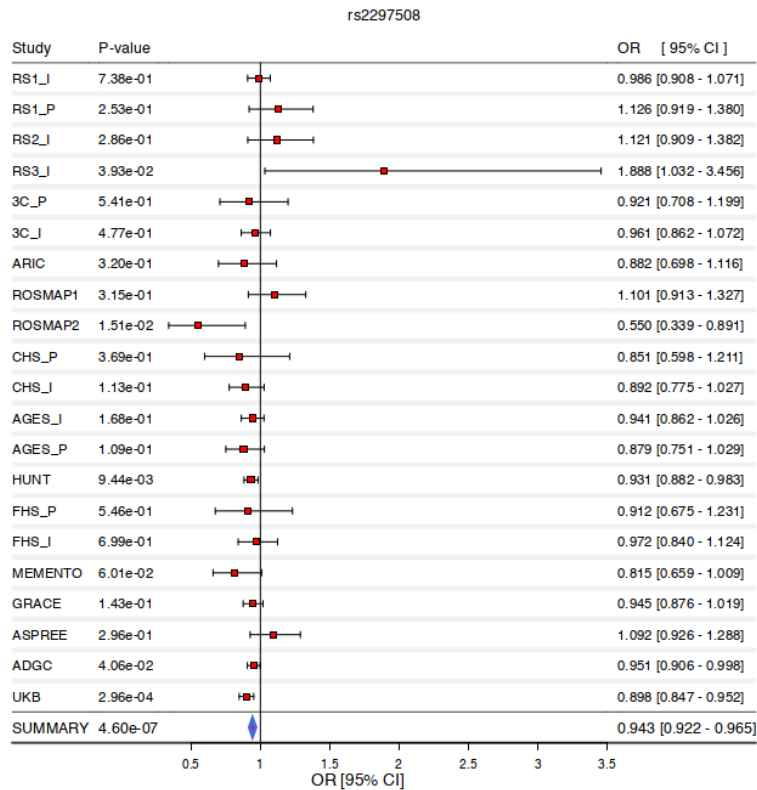


Figure S35: Forest plot of the locus near *SREBF1* in ACD GWAS of European ancestry.

2 – 2 – 7 INPP5D locus

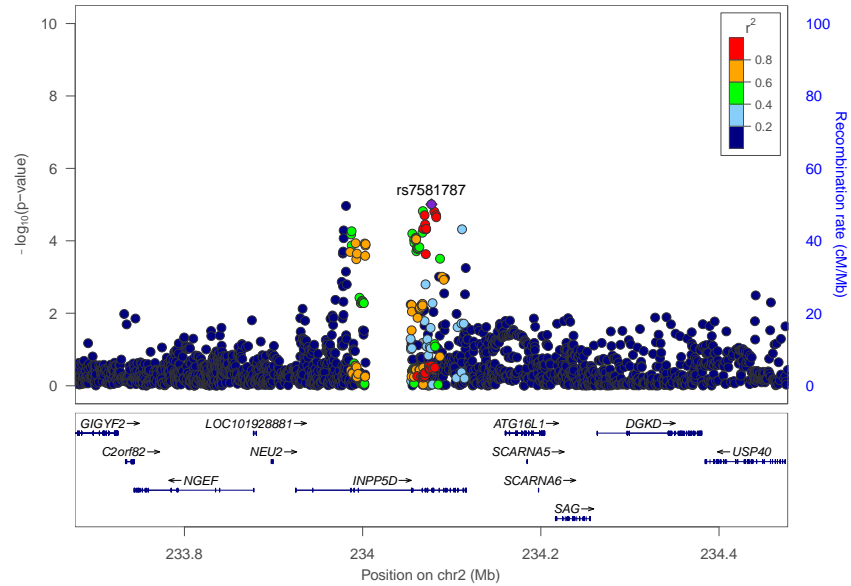


Figure S36: Regional association plot showing the genomic region containing INPP5D. For each SNP, the P-value (log10 scale) of the association with ACD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

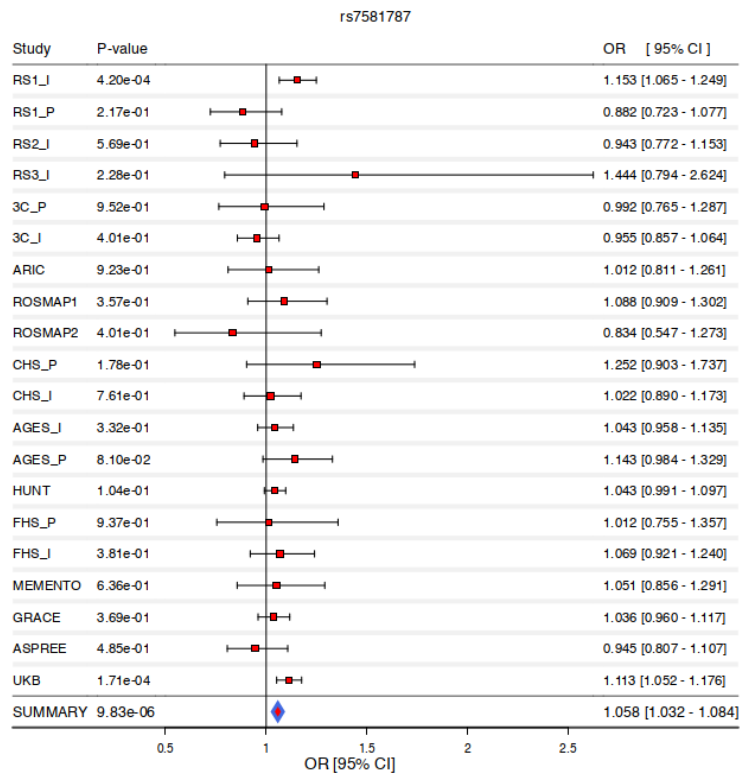


Figure S37: Forest plot of the locus near INPP5D in ACD GWAS of European ancestry.

2 – 3 Vascular dementia genome-wide significant variants
 2 – 3 – 1 APOE locus

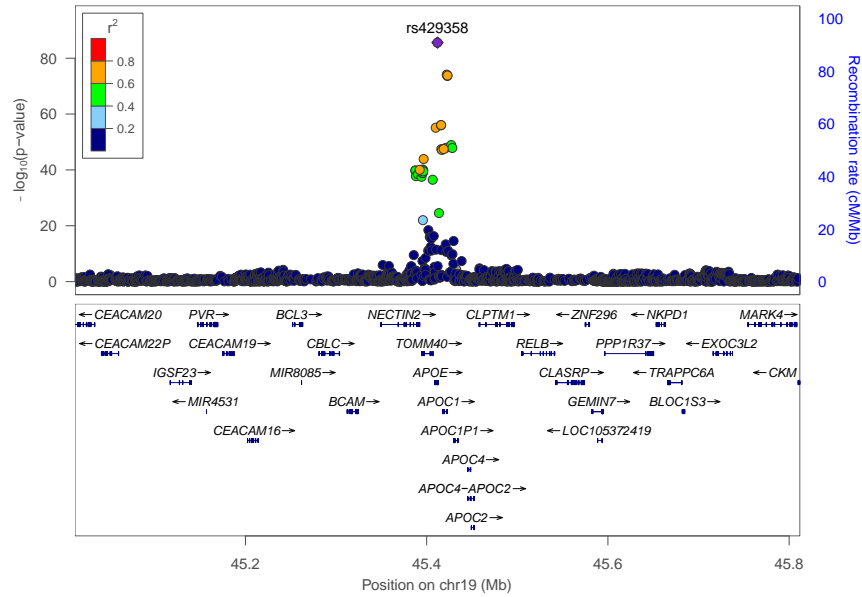


Figure S38: Regional association plot showing the genomic region containing INPP5D. For each SNP, the P-value (log10 scale) of the association with ACD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

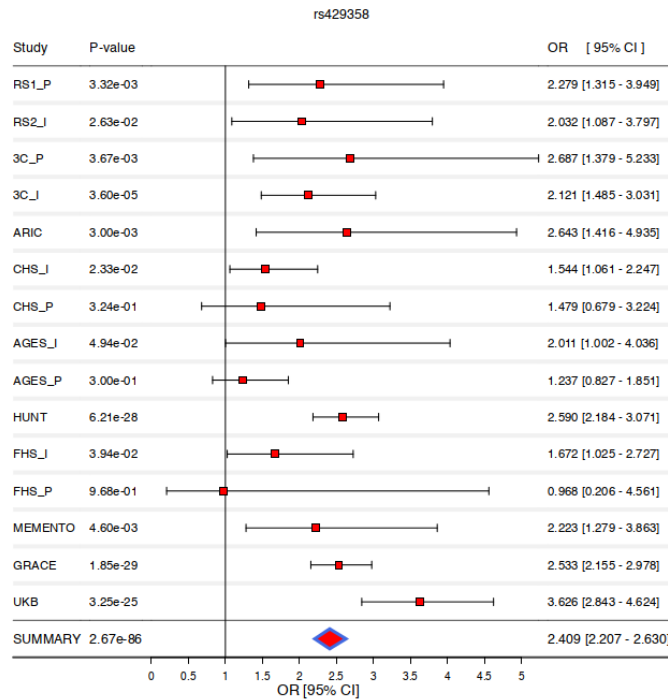


Figure S39: Forest plot of the locus near INPP5D in ACD GWAS of European ancestry.

2 – 4 Vascular dementia suggestive variants
 2 – 4 – 1 SPRY2 locus

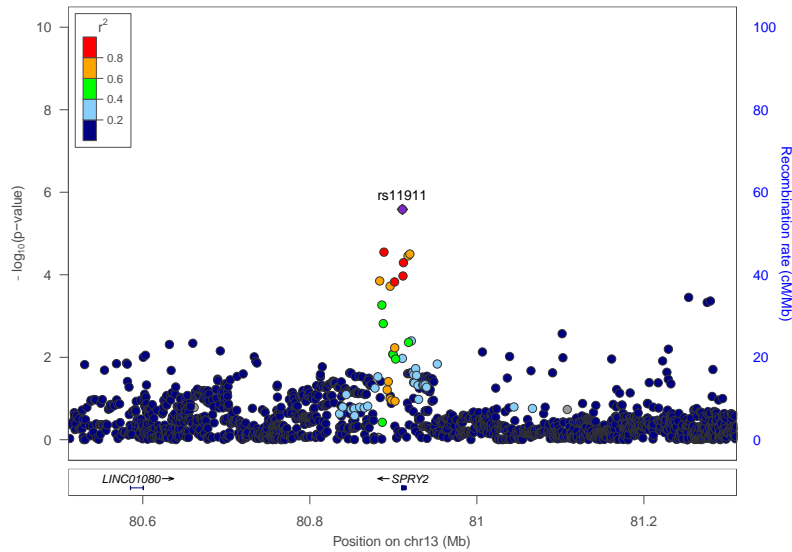


Figure S40: Regional association plot showing the genomic region containing **SPRY2**. For each SNP, the P-value (log10 scale) of the association with VaD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

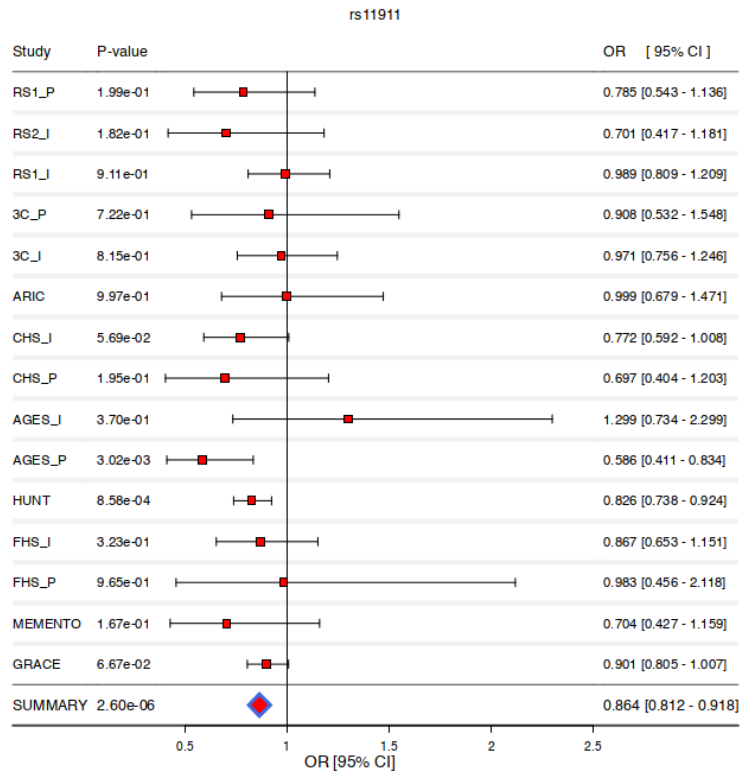


Figure S41: Forest plot of the locus near **SPRY2** in VaD GWAS of European ancestry.

2 – 4 – 2 SEMA6D locus

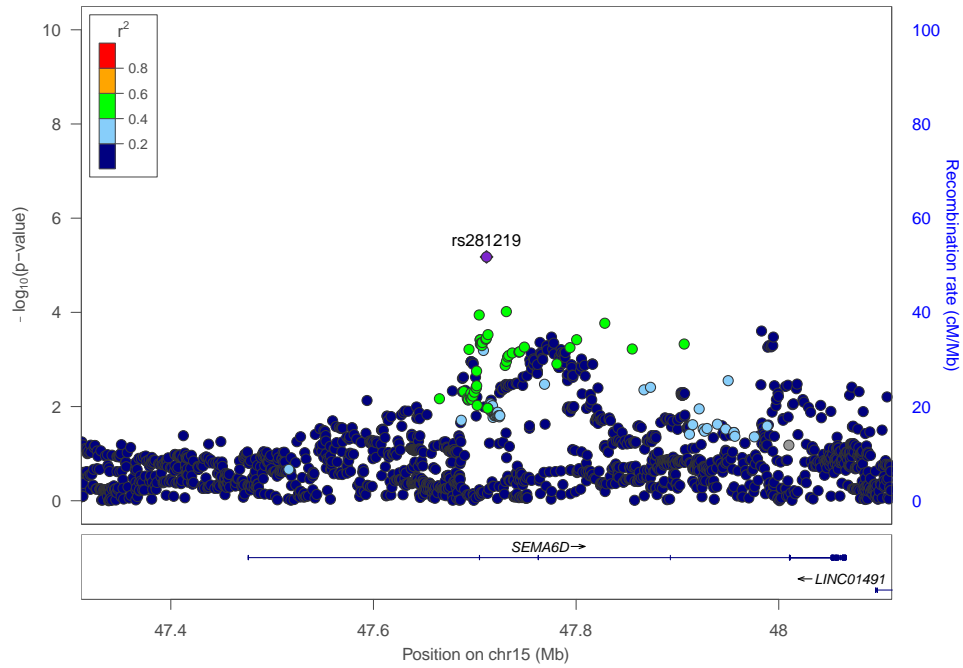


Figure S42: Regional association plot showing the genomic region containing **SEMA6D**. For each SNP, the P-value (log10 scale) of the association with VaD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

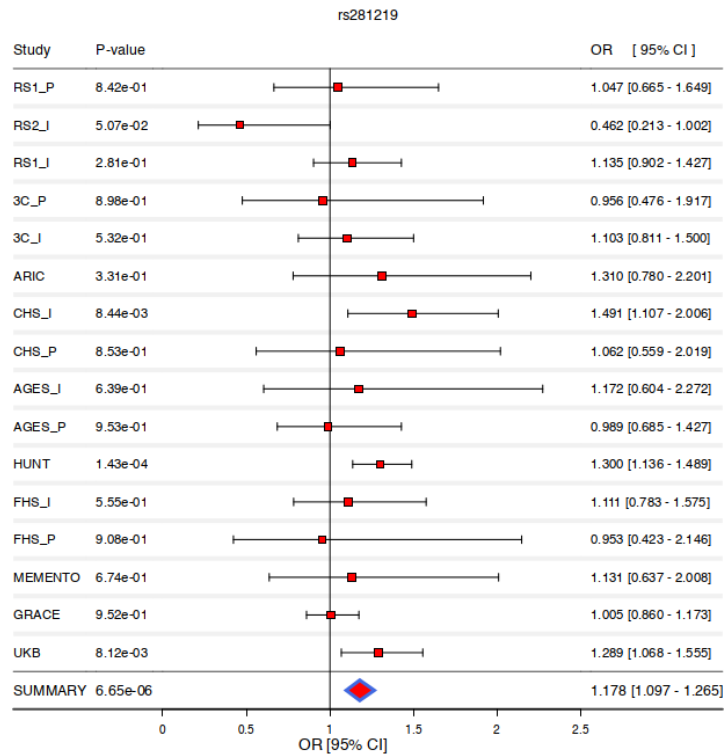


Figure S43: Forest plot of the locus near **SEMA6D** in VaD GWAS of European ancestry.

2 – 4 – 3 SCARB1 locus

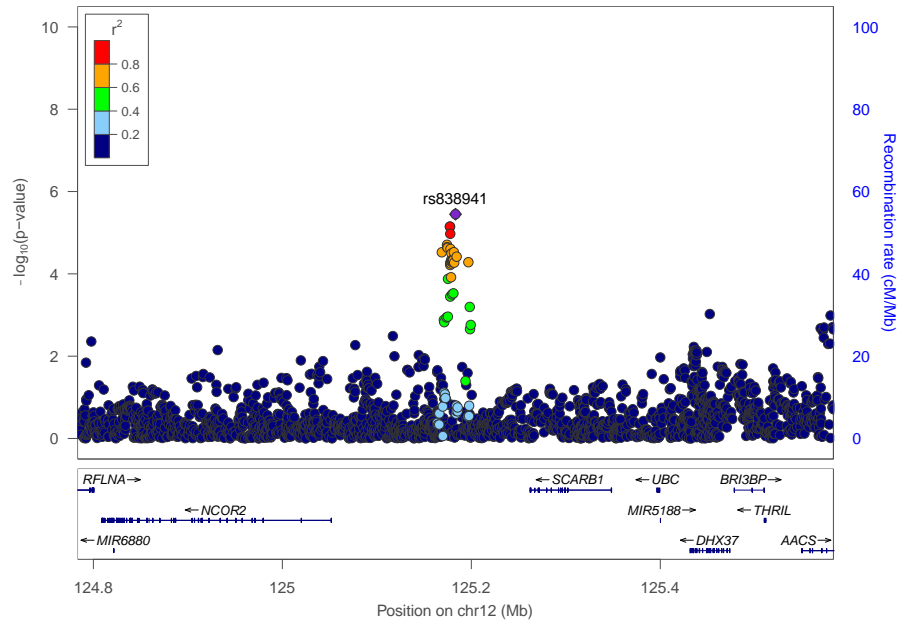


Figure S44: Regional association plot showing the genomic region containing *SCARB1*. For each SNP, the P-value (log10 scale) of the association with VaD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

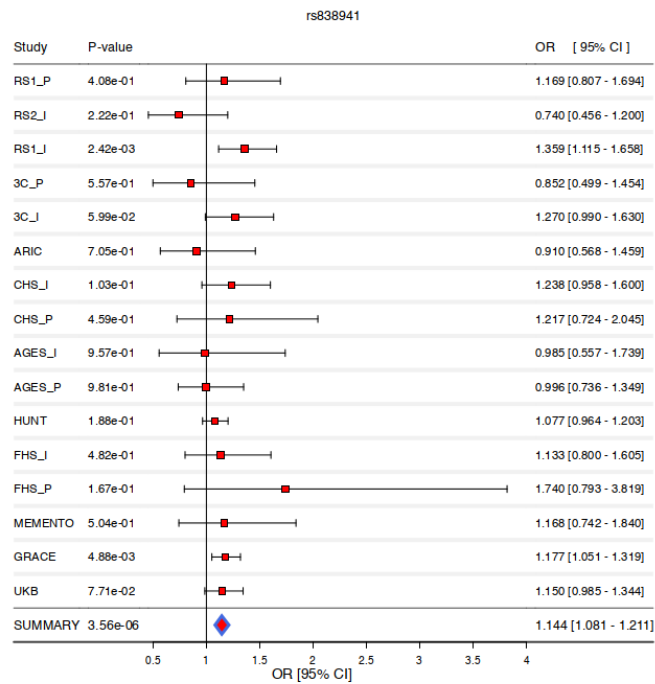


Figure S45: Forest plot of the locus near *SCARB1* in VaD GWAS of European ancestry.

2 – 4 – 4 PSMA3 locus

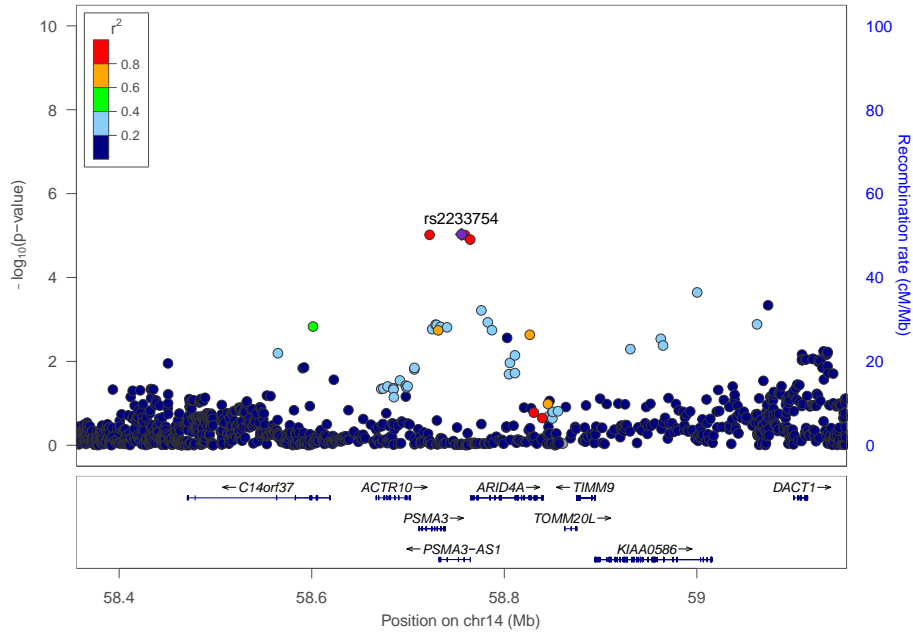


Figure S46: Regional association plot showing the genomic region containing **PSMA3**. For each SNP, the P-value (log10 scale) of the association with VaD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

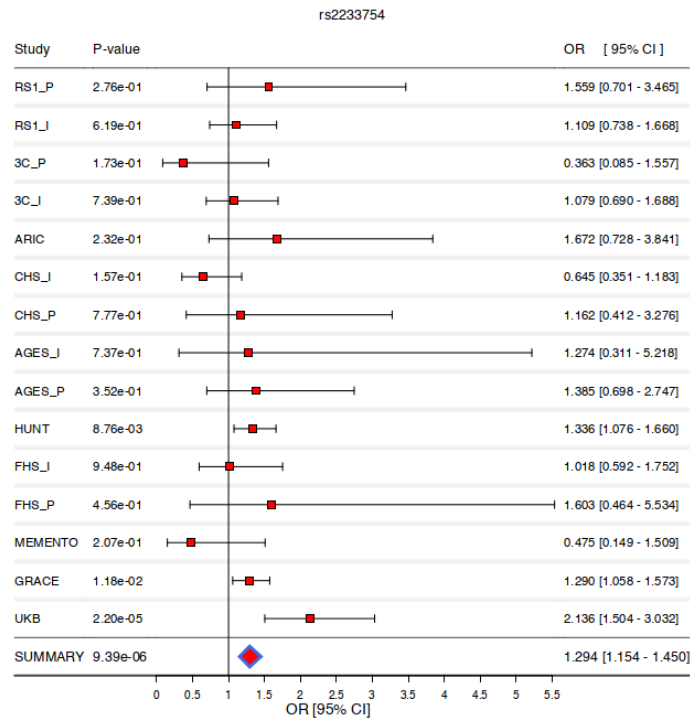


Figure S47: Forest plot of the locus near **PSMA3** in VaD GWAS of European ancestry.

2 – 4 – 5 LINC02113 locus

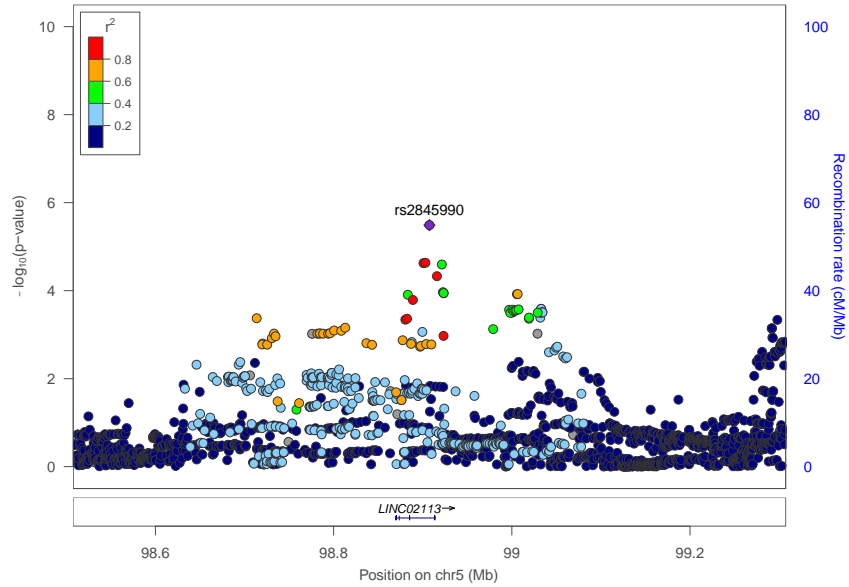


Figure S48: Regional association plot showing the genomic region containing LINC02113. For each SNP, the P-value (log10 scale) of the association with VaD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

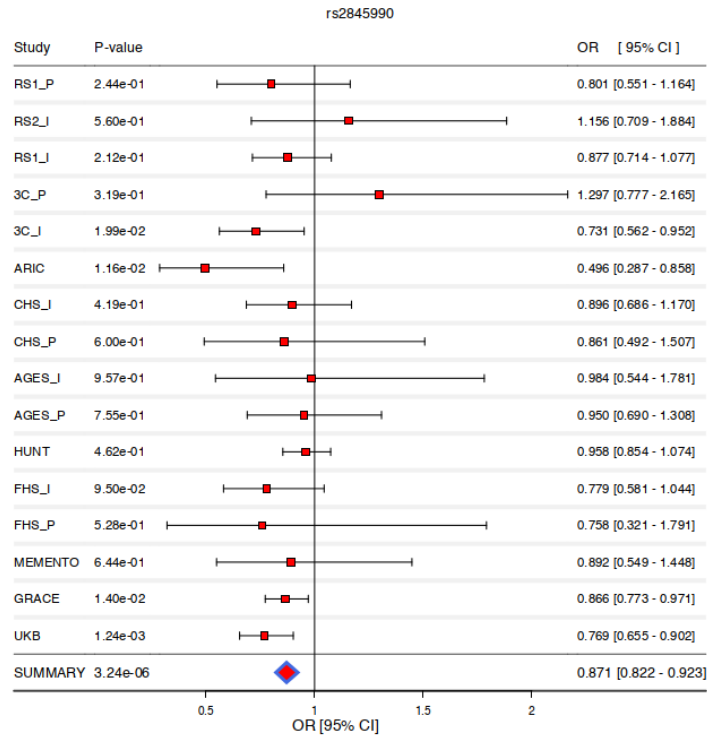


Figure S49: Forest plot of the locus near LINC02113 in VaD GWAS of European ancestry.

2 – 4 – 6 GIP locus

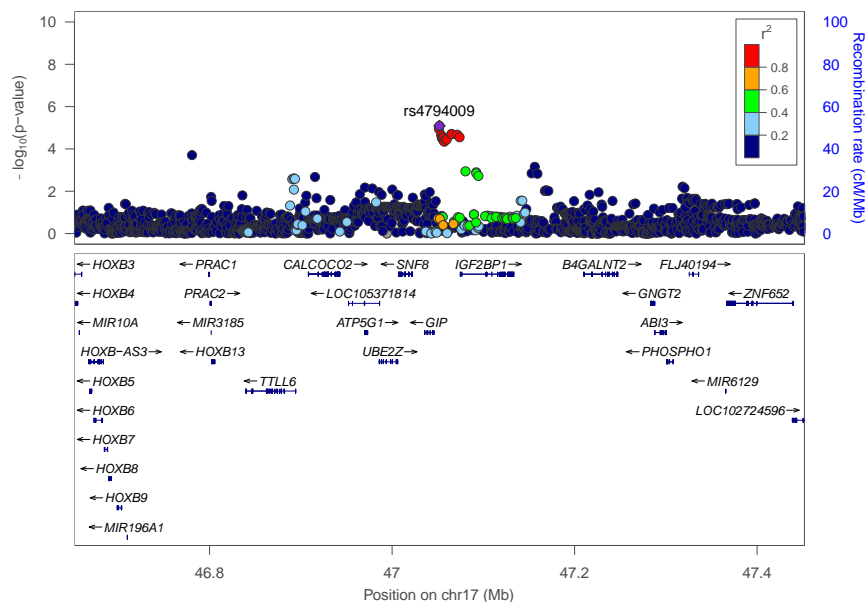


Figure S50: Regional association plot showing the genomic region containing GIP. For each SNP, the P-value (log₁₀ scale) of the association with VaD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

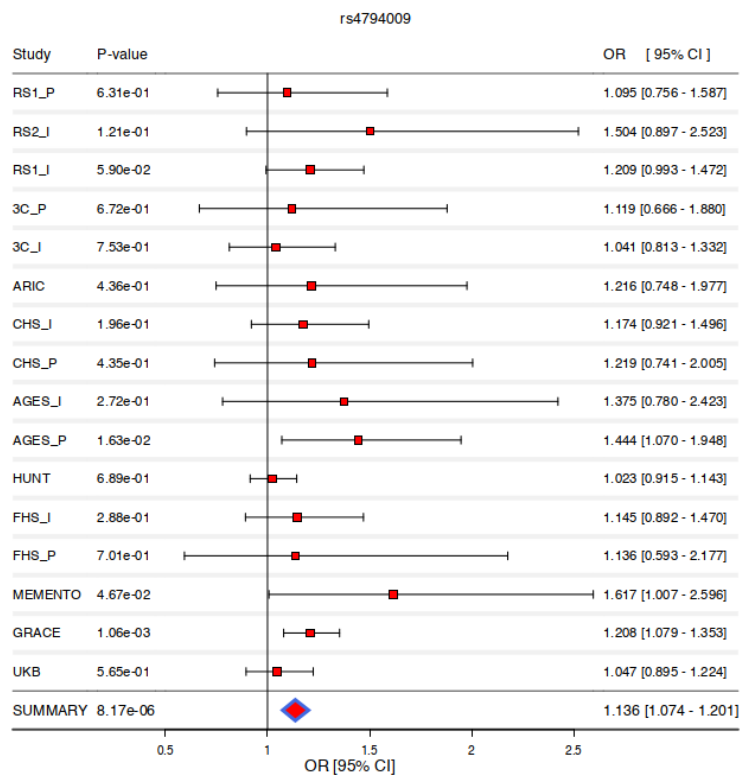


Figure S51: Forest plot of the locus near GIP in VaD GWAS of European ancestry.

2 – 4 – 7 DOK5 locus

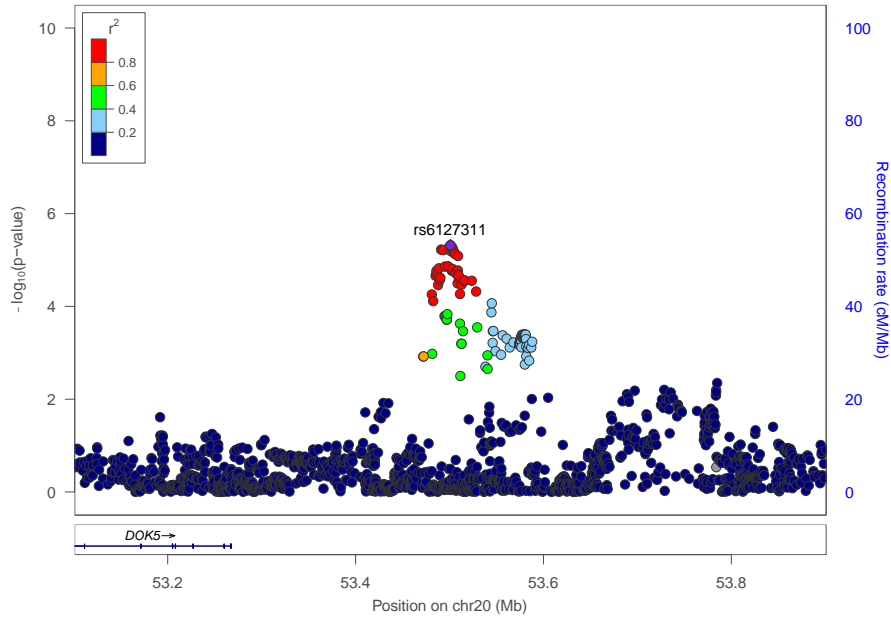


Figure S52: Regional association plot showing the genomic region containing *DOK5*. For each SNP, the P-value (log₁₀ scale) of the association with VaD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

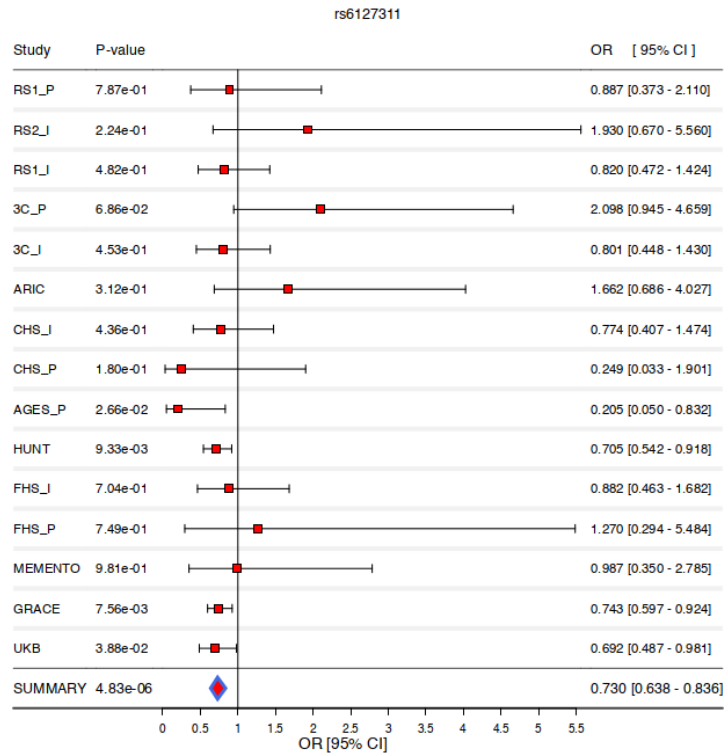


Figure S53: Forest plot of the locus near *DOK5* in VaD GWAS of European ancestry.

2 – 4 – 8 GALNT18 locus

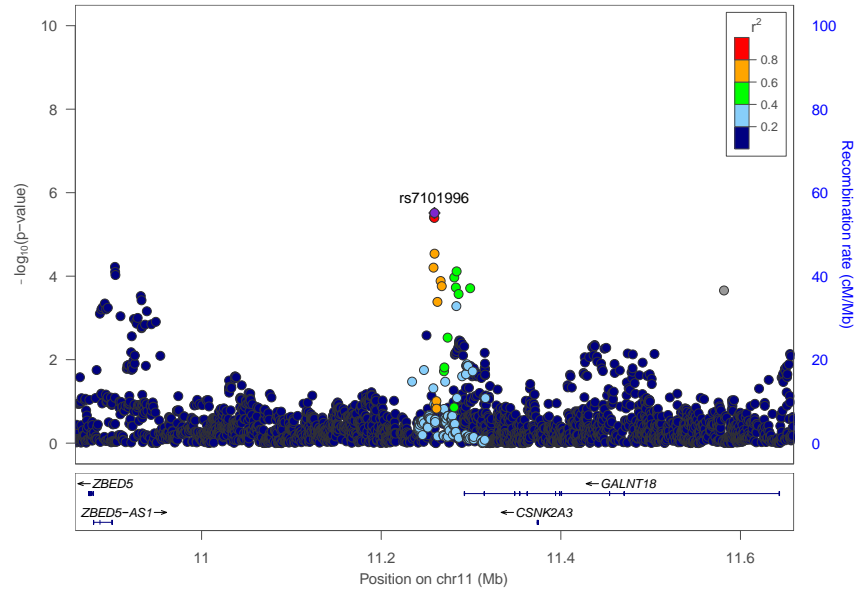


Figure S54: Regional association plot showing the genomic region containing **GALNT18**. For each SNP, the P-value (log10 scale) of the association with VaD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

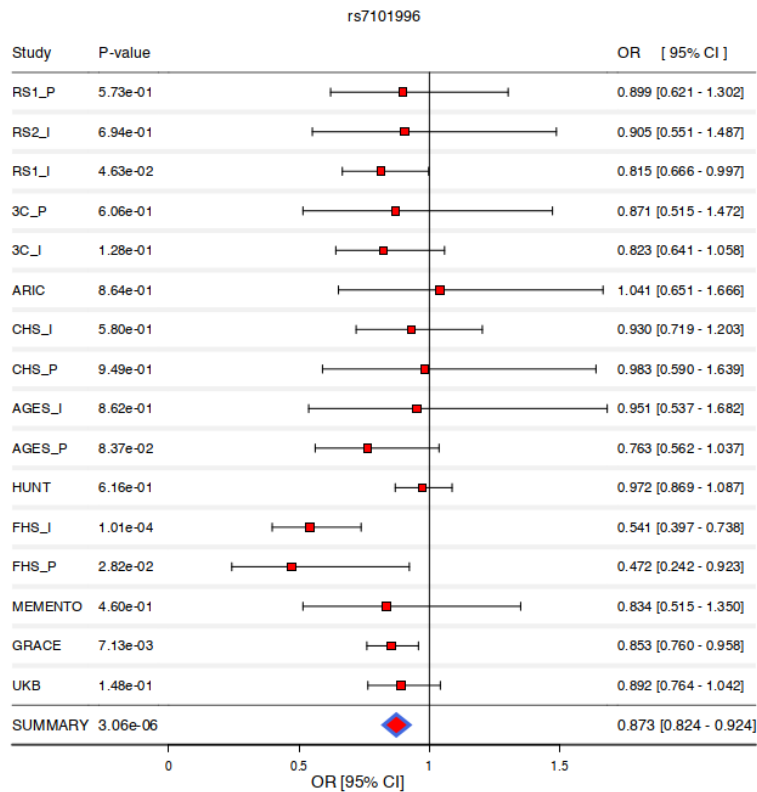


Figure S55: Forest plot of the locus near **GALNT18** in VaD GWAS of European ancestry.

2 – 4 – 9 WAC locus

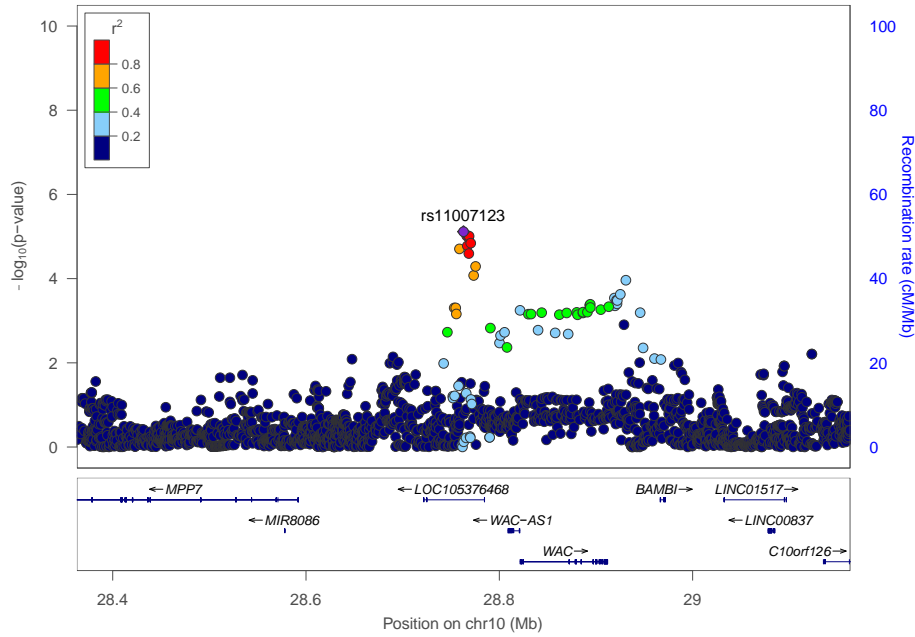


Figure S56: Regional association plot showing the genomic region containing WAC. For each SNP, the P-value (log₁₀ scale) of the association with VaD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

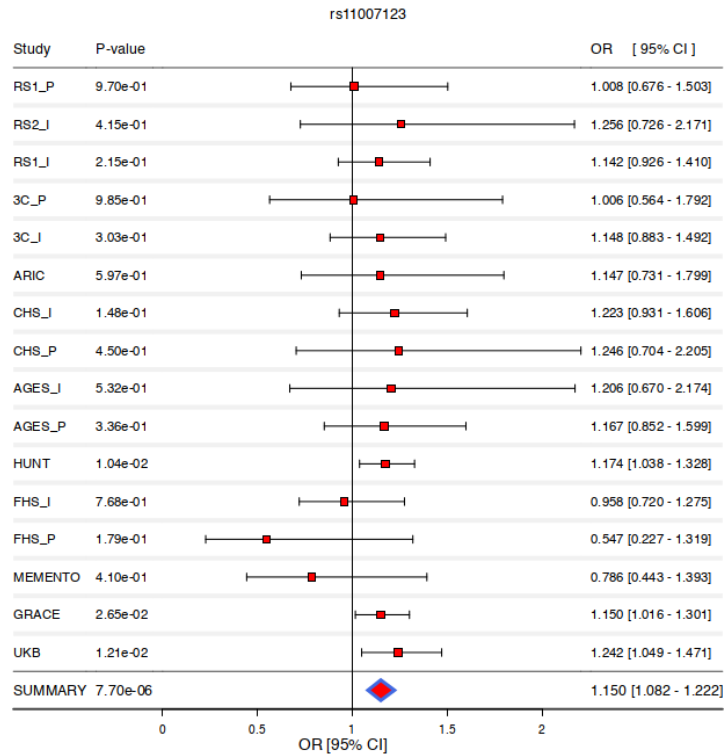


Figure S57: Forest plot of the locus near WAC in VaD GWAS of European ancestry.

2 – 4 – 10 ERBB4 locus

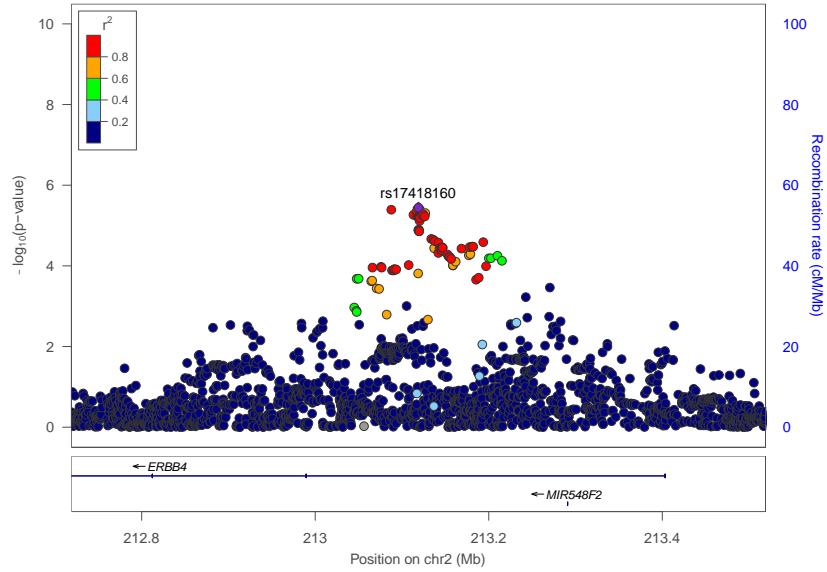


Figure S58: Regional association plot showing the genomic region containing ERBB4. For each SNP, the P-value (log10 scale) of the association with VaD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

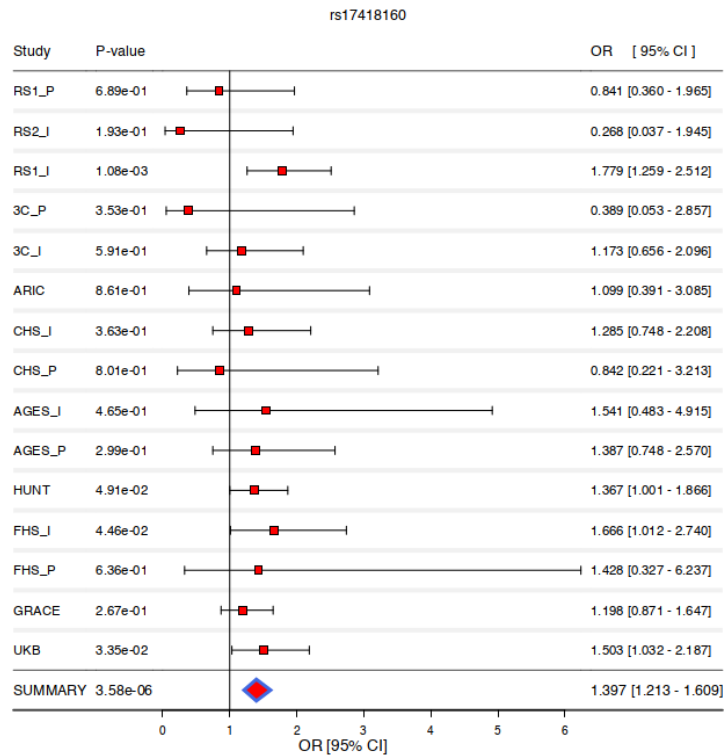


Figure S59: Forest plot of the locus near ERBB4 in VaD GWAS of European ancestry.

2 – 4 – 11 PRKCE locus

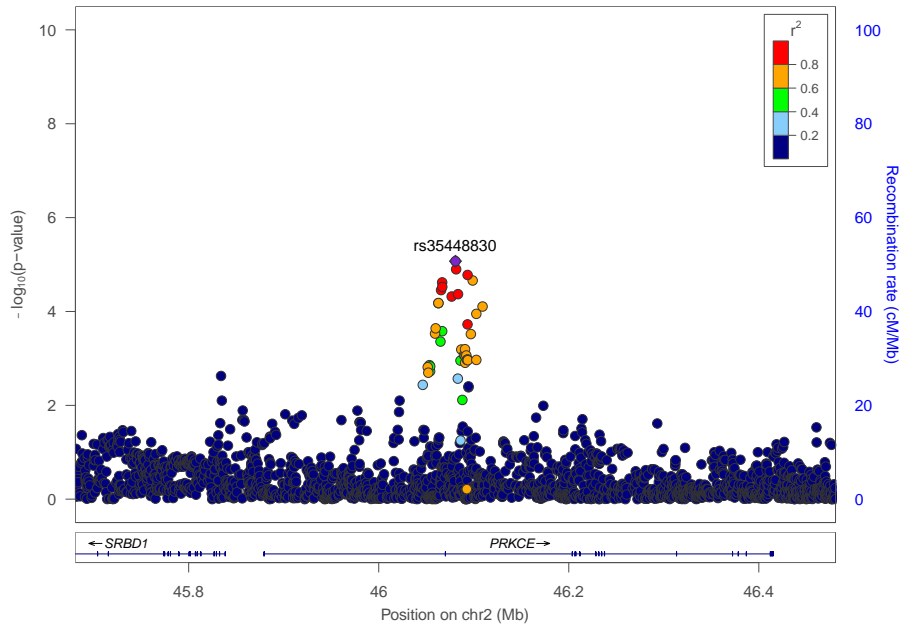


Figure S60: Regional association plot showing the genomic region containing PRKCE. For each SNP, the P-value (log10 scale) of the association with VaD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

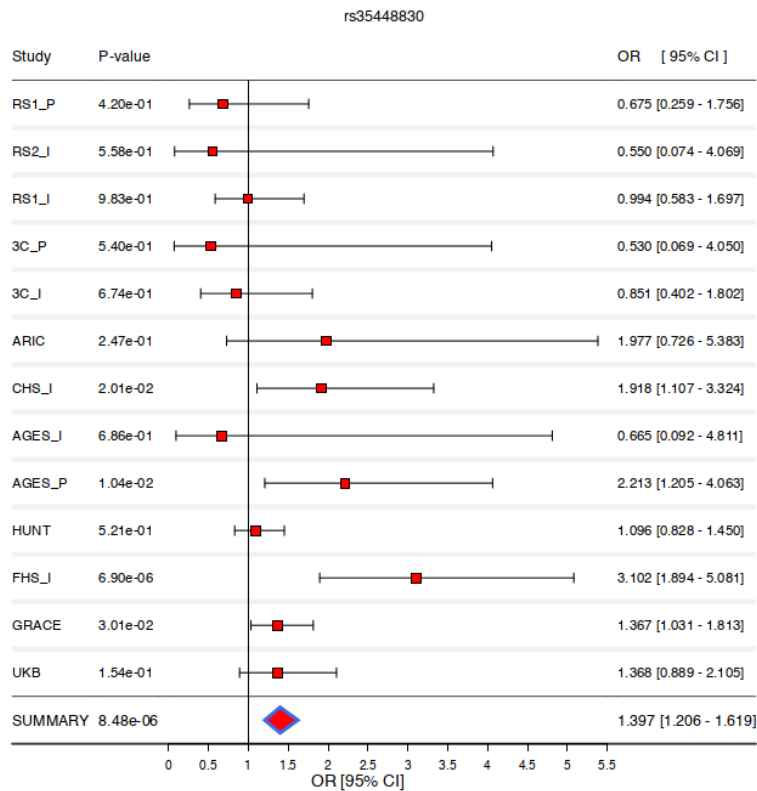


Figure S61: Forest plot of the locus near PRKCE in VaD GWAS of European ancestry.

2 – 4 – 12 PHACTR3 locus

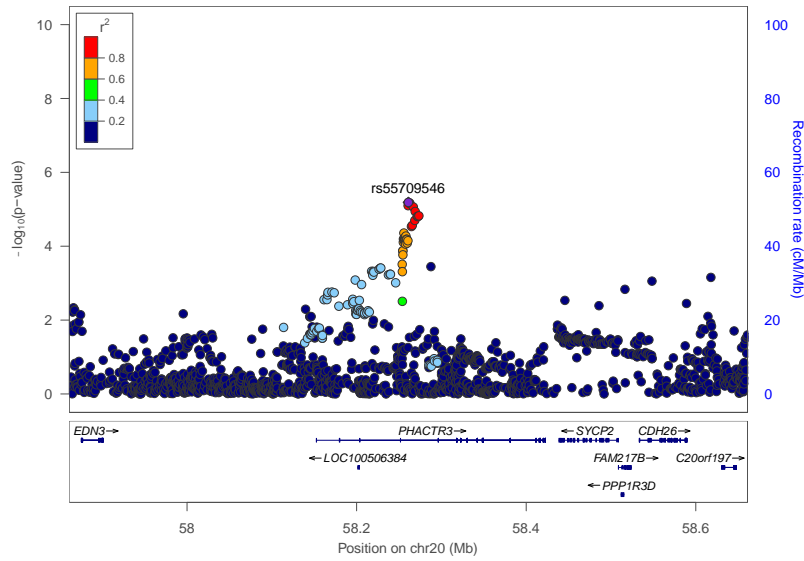


Figure S62: Regional association plot showing the genomic region containing PHACTR3. For each SNP, the P-value (log10 scale) of the association with VaD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted

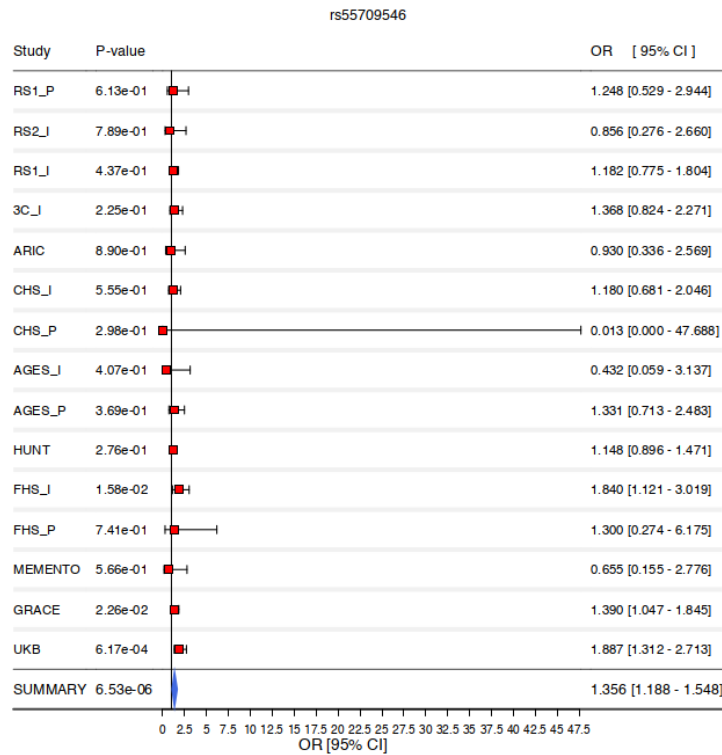


Figure S63: Forest plot of the locus near PHACTR3 in VaD GWAS of European ancestry.

2 – 4 – 13 AJAP1 locus

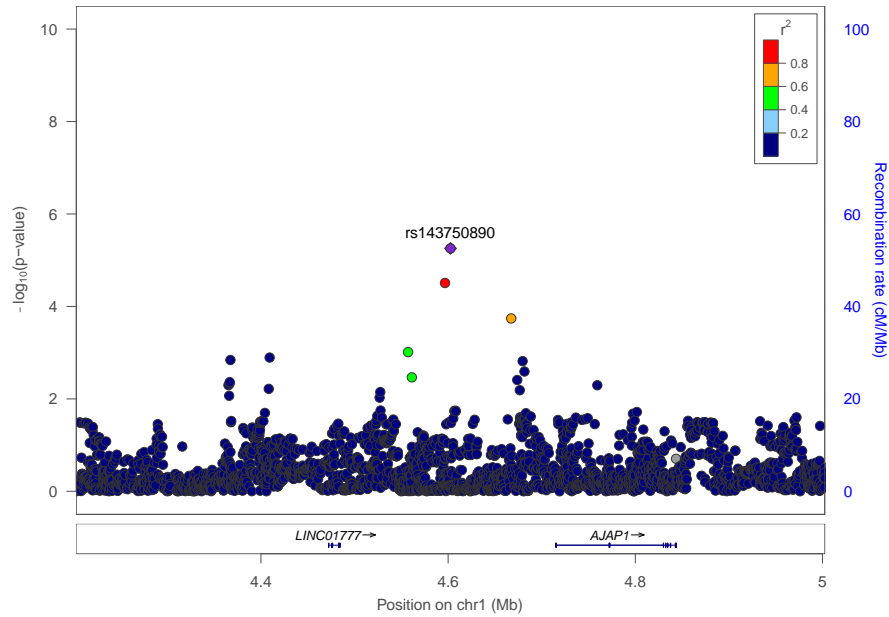


Figure S64: Regional association plot showing the genomic region containing **AJAP1**. For each SNP, the P-value (log10 scale) of the association with VaD is represented (y-axis, left). The recombination rates (y-axis right), which reflect the local linkage disequilibrium structure, are also plotted.

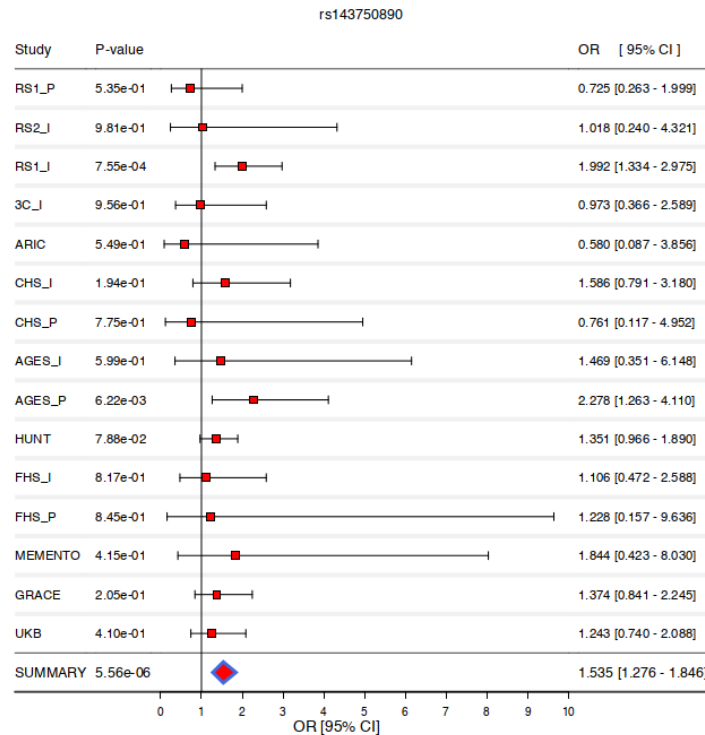


Figure S65: Forest plot of the locus near **AJAP1** in VaD GWAS of European ancestry.

2 – 5 Cross-Ancestry meta-analysis plots

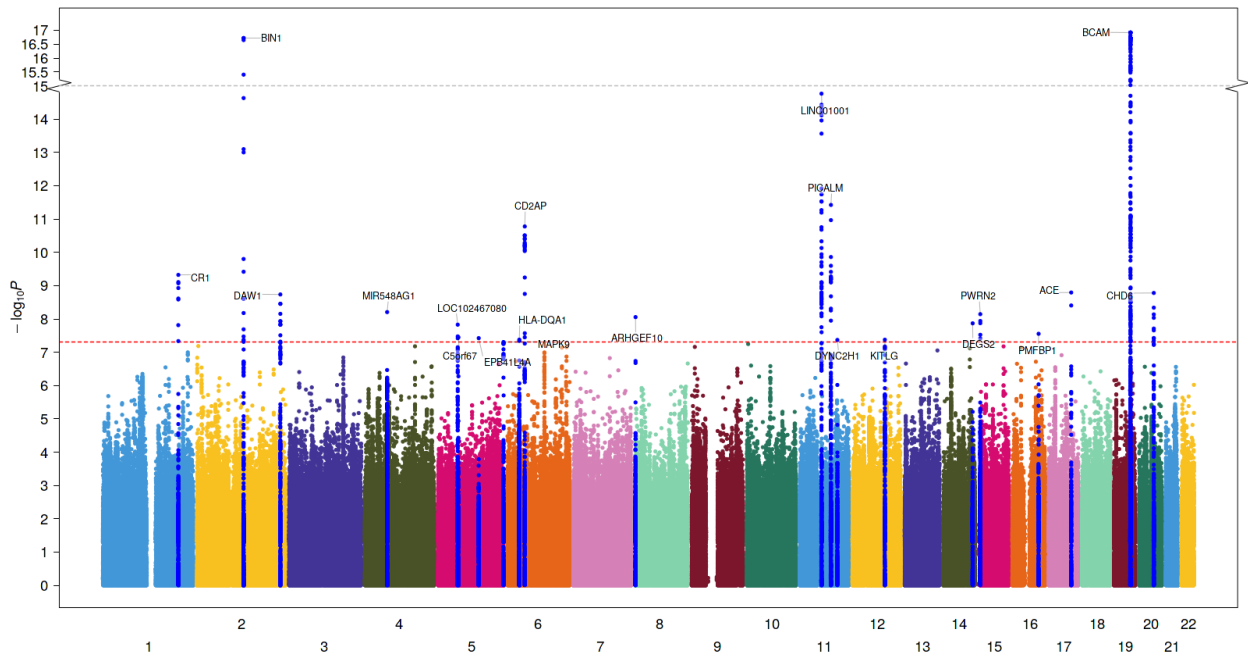


Figure S66: Manhattan plot of the trans-ancestral meta-analysis of ACD GWASs. In addition to variants in the APOE region, we identified five new genetic loci associated with VaD. Blue and red lines correspond to the p-value of $5e^{-7}$ and $5e^{-8}$ for genome-wide suggestive and significant SNPs, respectively. Manhattan plots for the cross-ancestry meta-analysis. Each dot represents a SNP, the X-axis shows the chromosomes where each SNP is located, and the Y-axis shows $-\log_{10}$ P-value of the association of each SNP with POAG in the cross-ancestry meta-analysis. The red horizontal line shows the genome-wide significant threshold (P-value= $5e^{-8}$; $-\log_{10}$ P-value=7.30). The nearest gene to the most significant SNP in each locus has been labeled.

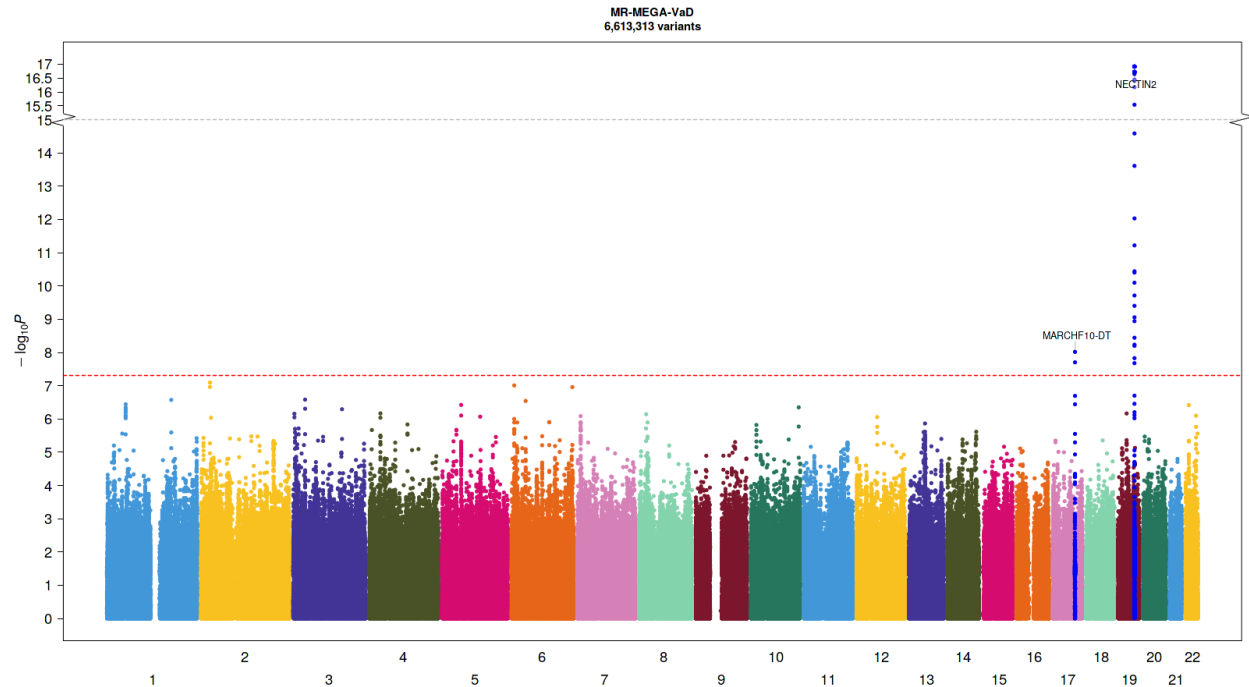


Figure S67: Manhattan plot of the trans-ancestral meta-analysis of VaD GWASs. In addition to variants in the APOE region, we identified five new genetic loci associated with VaD. Blue and red lines correspond to the p-value of $5e^{-7}$ and $5e^{-8}$ for genome-wide suggestive and significant SNPs, respectively. Manhattan plots for the cross-ancestry meta-analysis. Each dot represents a SNP, the X-axis shows the chromosomes where each SNP is located, and the Y-axis shows $-\log_{10}$ P-value of the association of each SNP with POAG in the cross-ancestry meta-analysis. The red horizontal line shows the genome-wide significant threshold (P-value= $5e^{-8}$; $-\log_{10}$ P-value=7.30). The nearest gene to the most significant SNP in each locus has been labeled.

3 – Other Figures

3 – 1 Variant Overlap with other complex traits

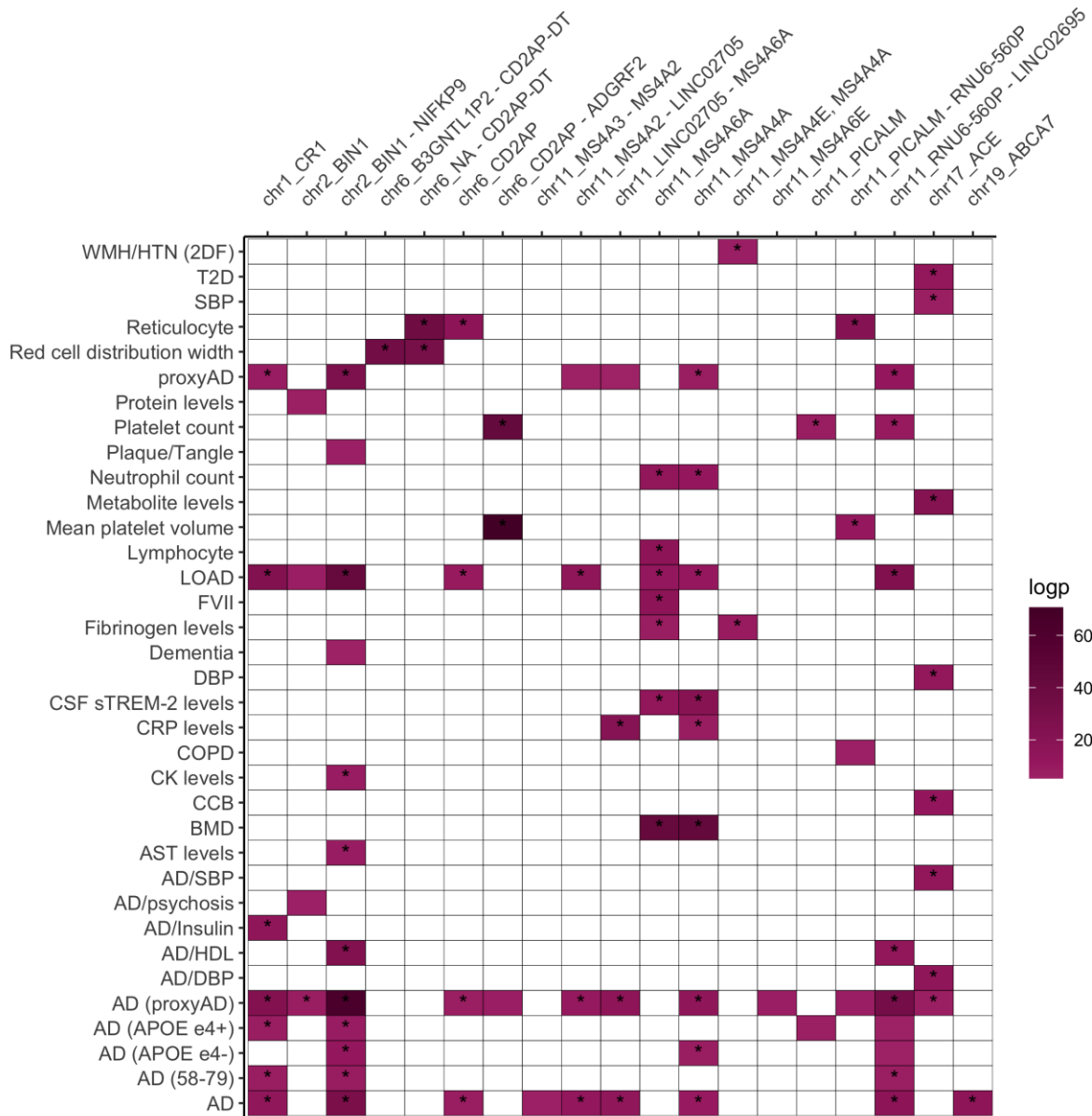


Figure S68: Variant level overlap with complex disease traits

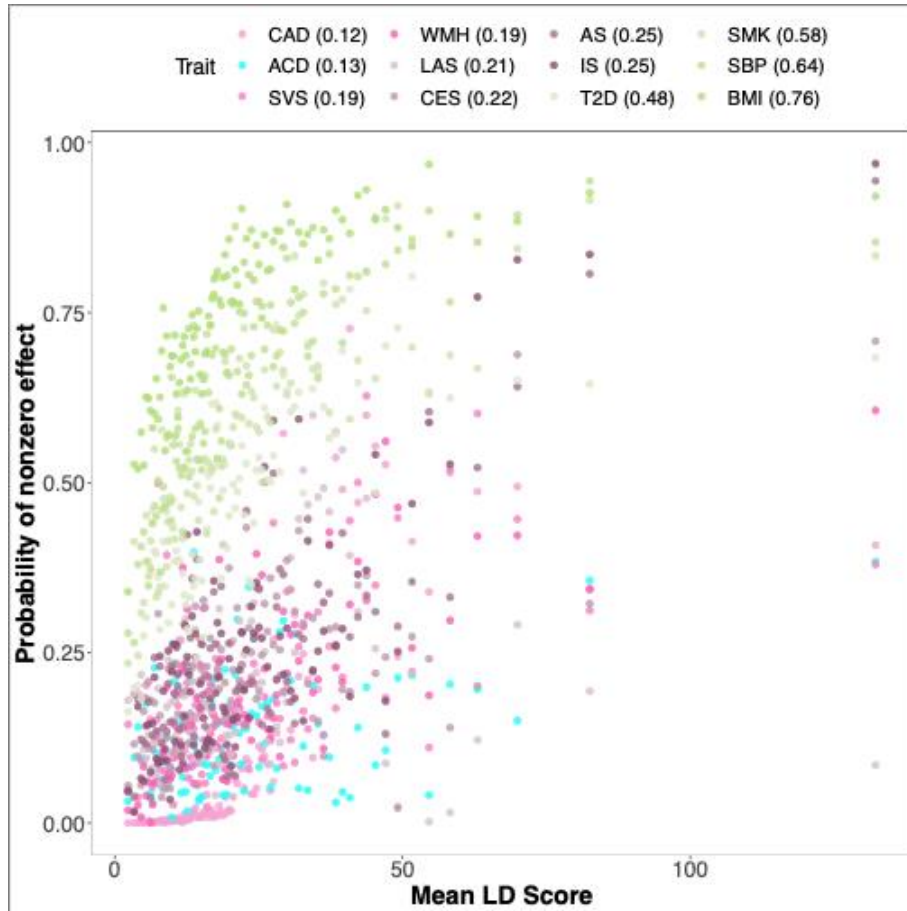


Figure S69: Non-zero effect distribution of ACD and other complex disease traits

3 – 2 Functional analysis Figures

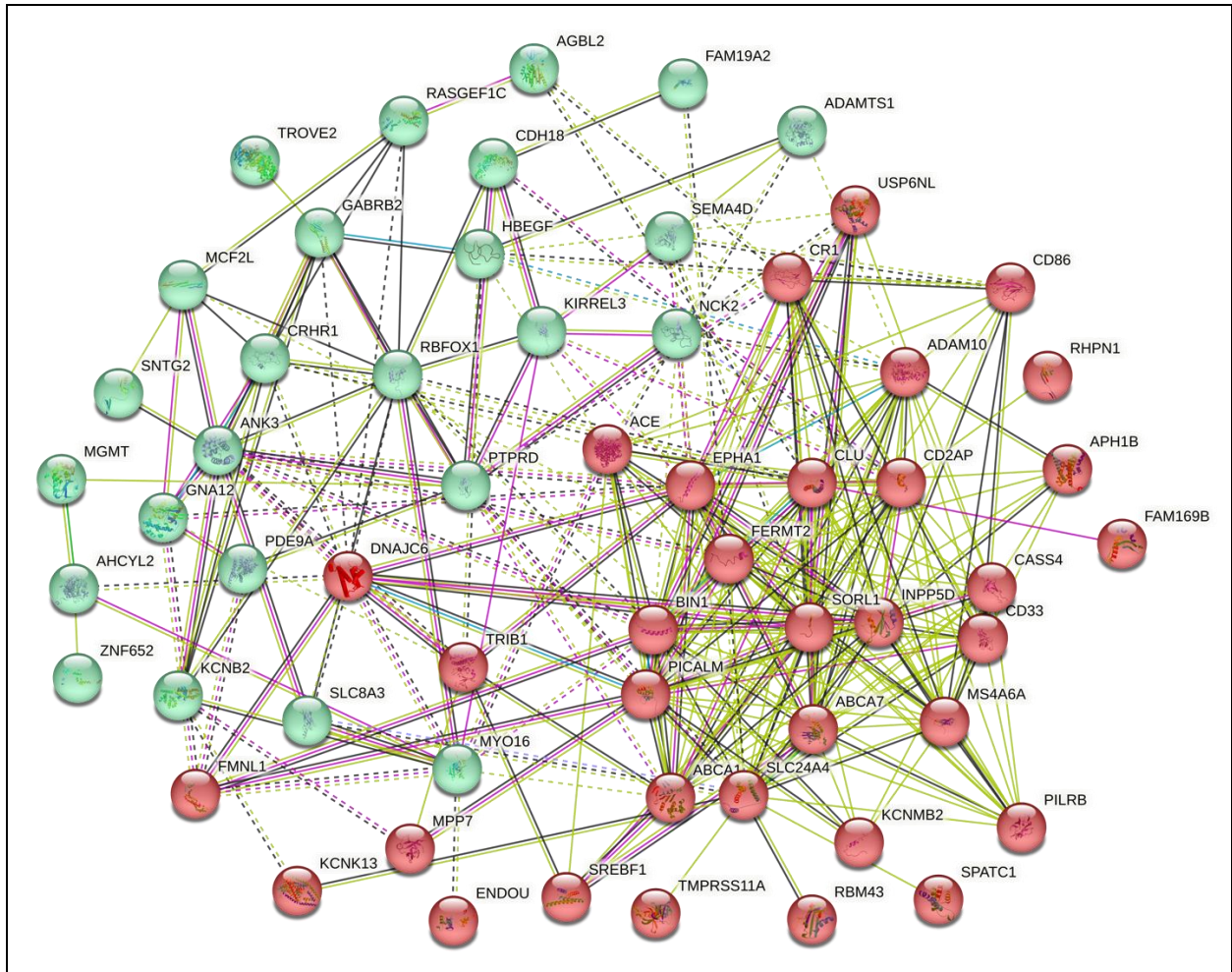


Figure S70: STRING clustering of ACD genes. The hierarchical clustering of ACD in two groups provides insights into the potential interactions between prominent genes. The red cluster is highly enriched in known AD-related genes, while the green cluster mostly included our ACD-suggestive genes.

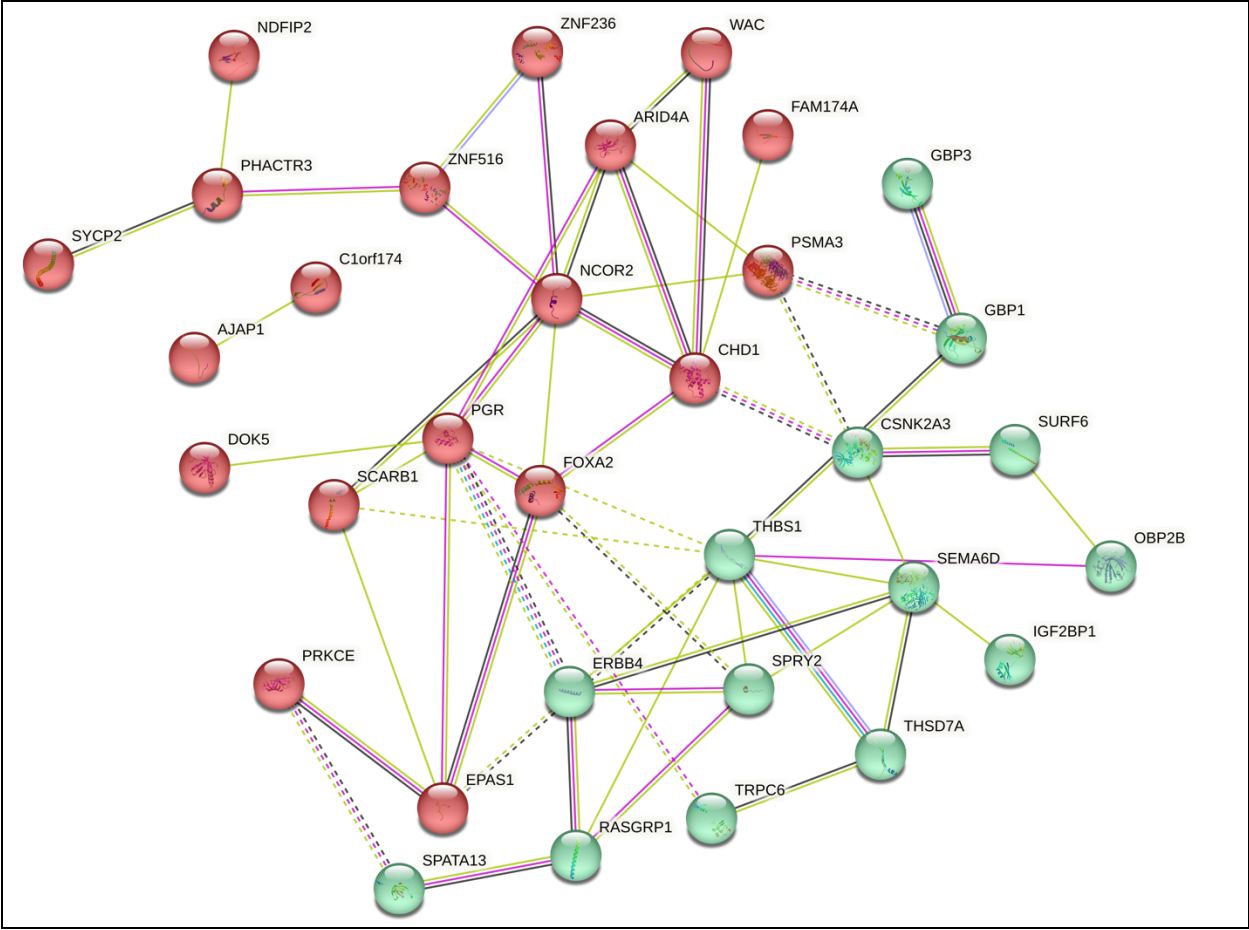


Figure S71: STRING clustering of VaD genes. The hierarchical clustering of VaD in two groups provides insights into the potential interactions between prominent genes.

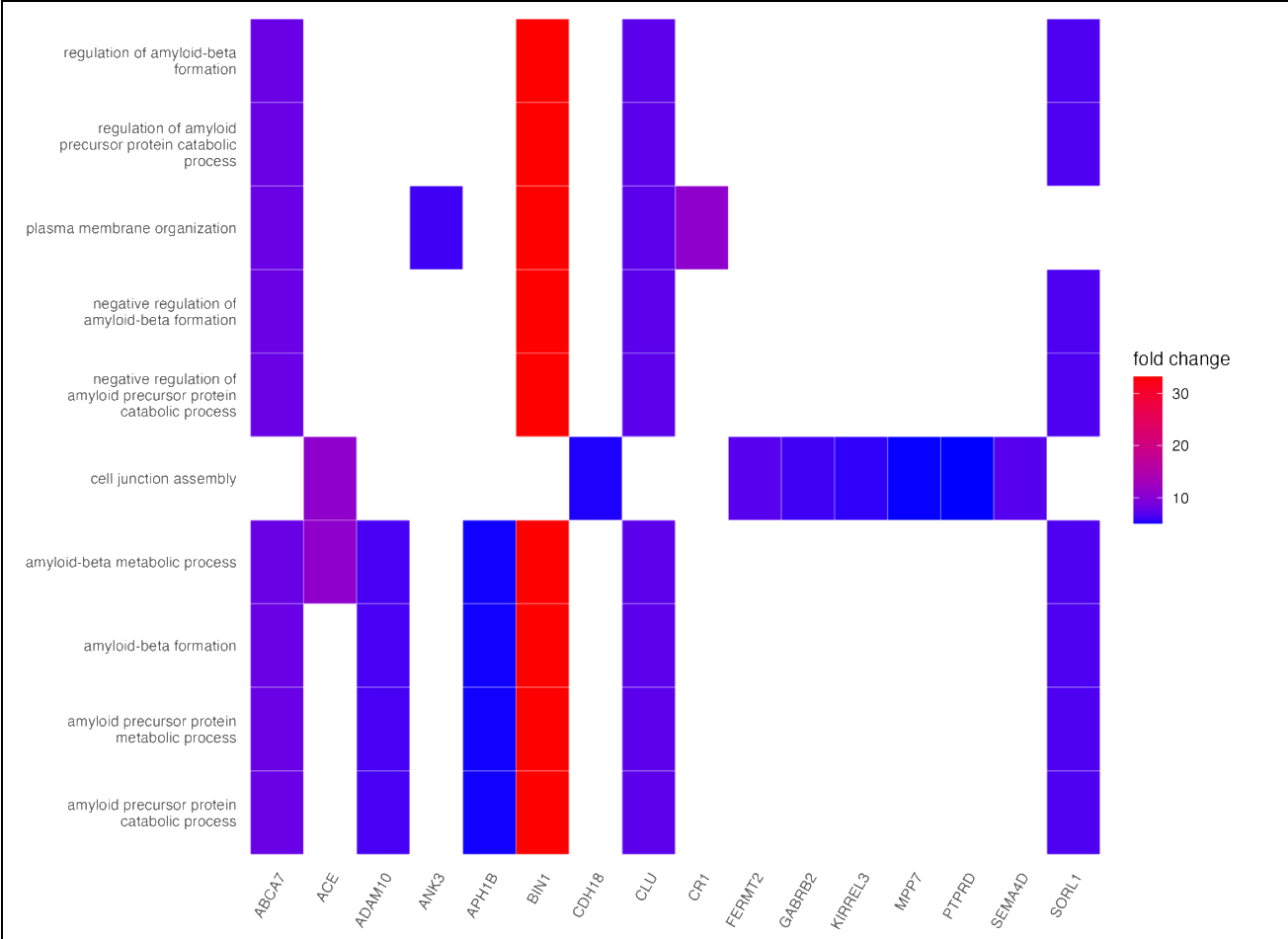


Figure S72: ACD Gene Ontology (GO) analysis, Biological Processes.

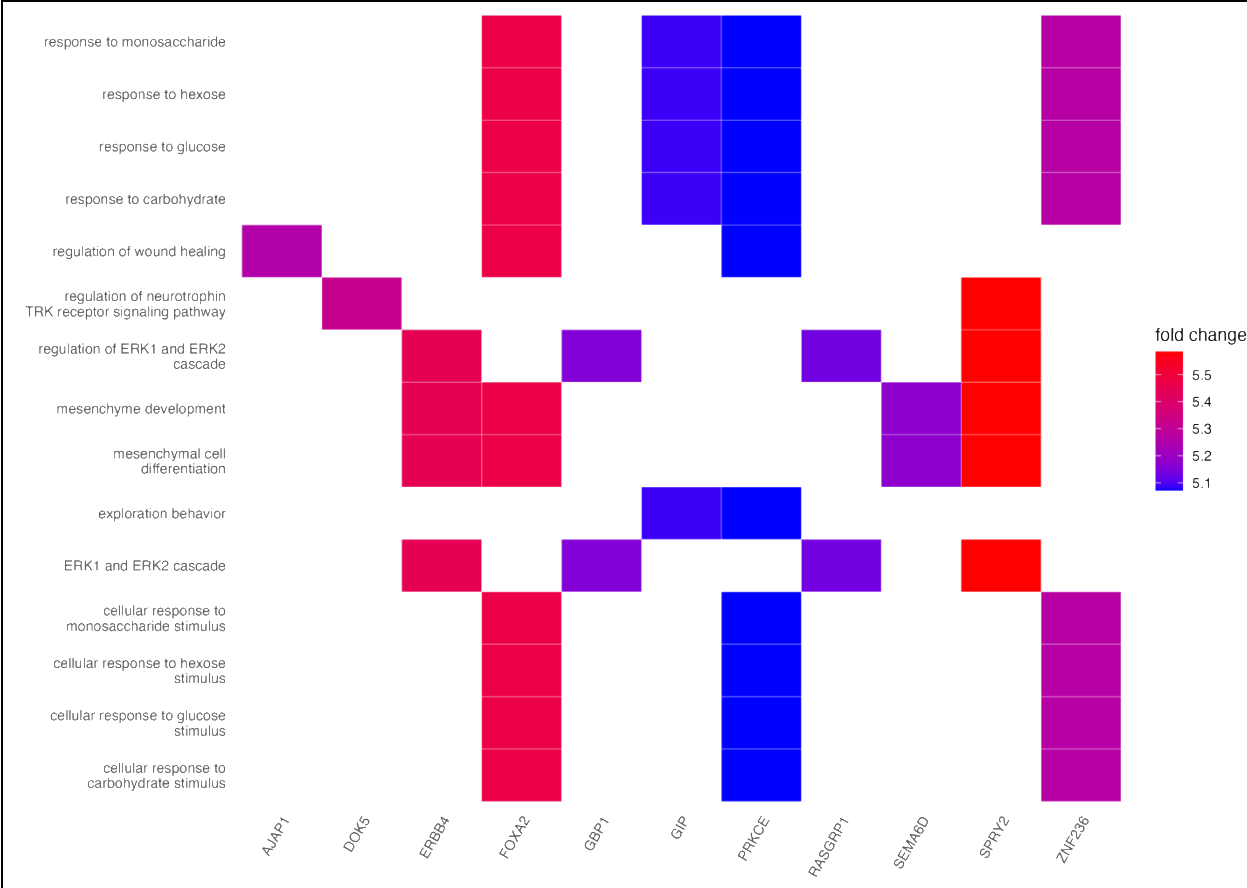


Figure S73: VaD Gene Ontology (GO) analysis, Biological Processes.

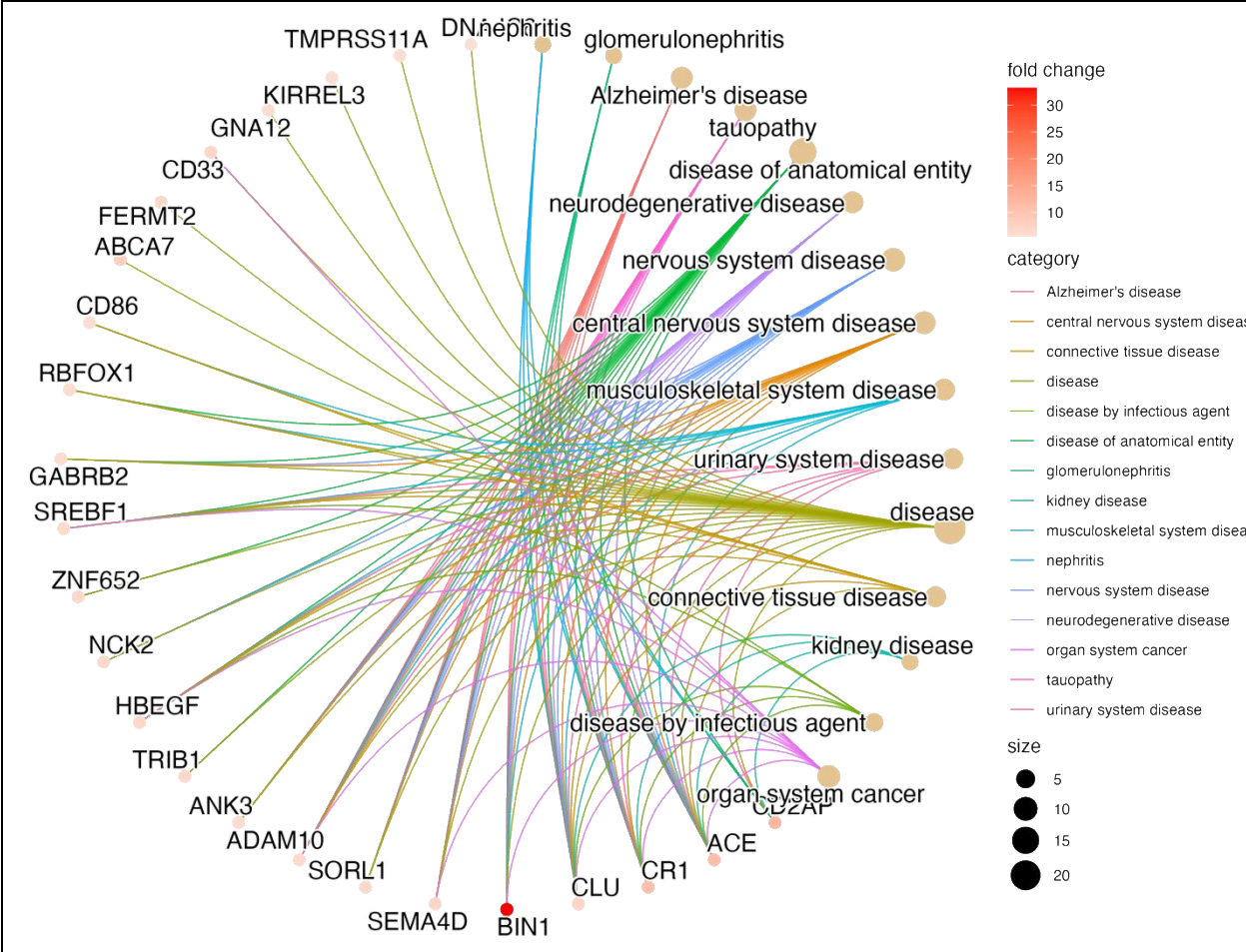


Figure S74: ACD disease association analysis

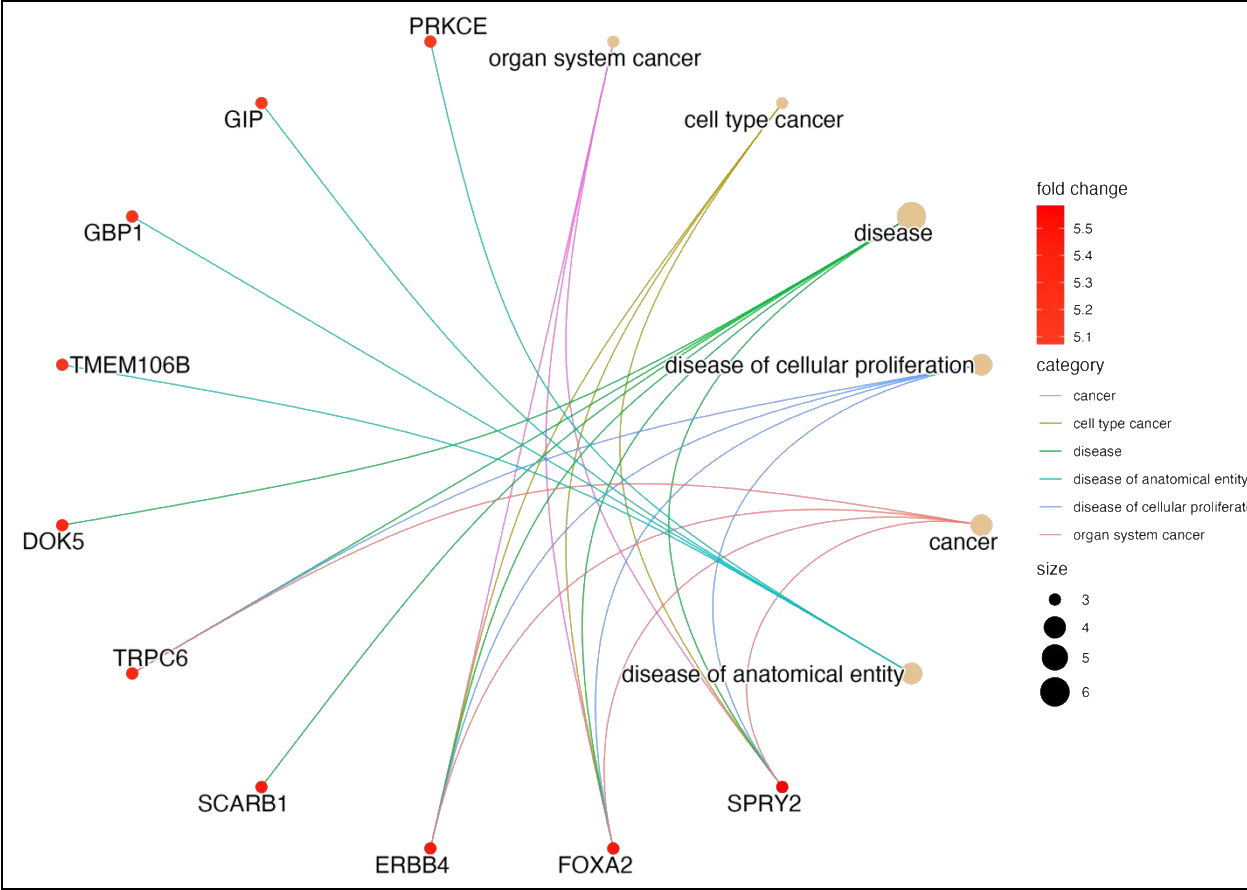


Figure S75: VaD disease association analysis.