**MMP-degraded type I collagen is associated with APOE/TOMM40 variants and preclinical dementia**

Tang MH1\*, Blair JPM1, 2, Bager CL1, Bay-Jensen AC3, Henriksen K4, Christiansen C3, Karsdal MA3.

1 ProScion, Herlev, Denmark

2 University of Copenhagen, Faculty of Health and Medical Sciences, Copenhagen, Denmark

3 ImmunoScience, Nordic Bioscience, Biomarkers and Research, Herlev, Denmark

4 Endocrinology, Nordic Bioscience, Biomarkers and Research, Herlev, Denmark

\*Corresponding author:

Dr. Man-Hung Eric Tang

ProScion, Herlev Hovedgade 205-207

DK-2730

Herlev, Denmark

E-mail: met@nordicbio.com

# **Supplementary figures**

A close up of a logo

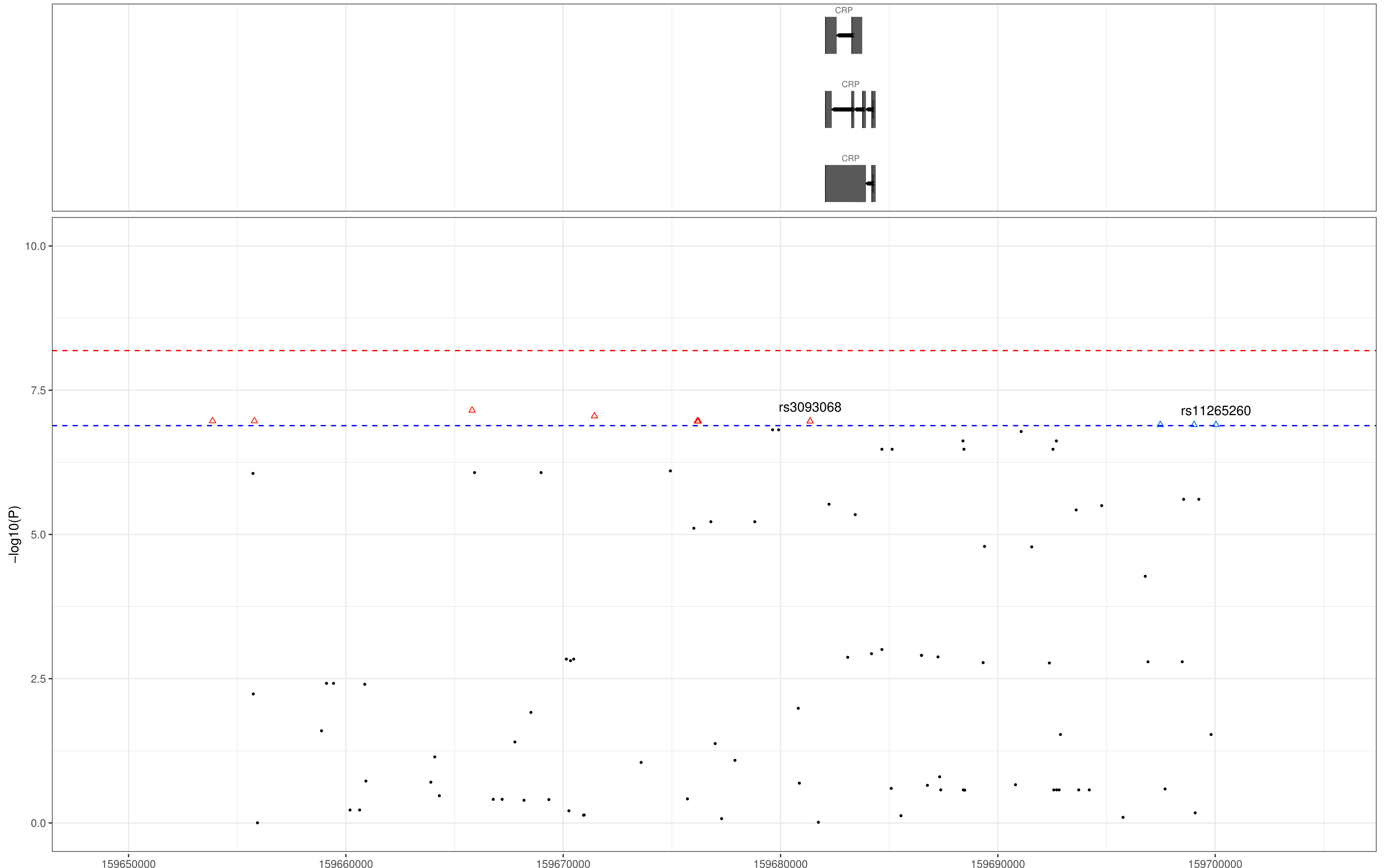
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**Figure e-1:** Study participant inclusion flowchart.

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**Figure e-2:** Zoomed-in Manhattan plot of the chr19 APOE-C1/TOMM40 gene locus for GWAS screen for association with the biomarker C1M. The red and blue dotted-lines show the genome-wide and suggestive significance cut-offs, adjusted to the number of tests (6.5e-9 and 1.3e-7 respectively). Downward-pointing symbols indicate negative and upward-pointing symbols positive effect sizes of the association to the SNP. Symbols of the same color are in linkage between each other. Non-significant association are shown as small black dots.

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**Figure e-3:** Zoomed-in Manhattan plot of the chr1 CRP gene locus of the GWAS screen for association with the biomarker C1M. The red and blue dotted-lines show the genome-wide and suggestive significance cut-offs, adjusted to the number of tests (6.5e-9 and 1.3e-7 respectively). Downward-pointing symbols indicate negative and upward-pointing symbols positive effect sizes of the association to the SNP. Symbols of the same color are in linkage between each other. Non-significant association are shown as small black dots.

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**Figure e-4:** Linkage Disequilibrium of the significant associations with C1M.  
Variants in the plot are sorted in their genomic order and chromosome and satisfy the standard suggestive association threshold. Chromosome number and effect-size of the associations with C1M is shown on the horizontal annotation bar.

A close up of a logo

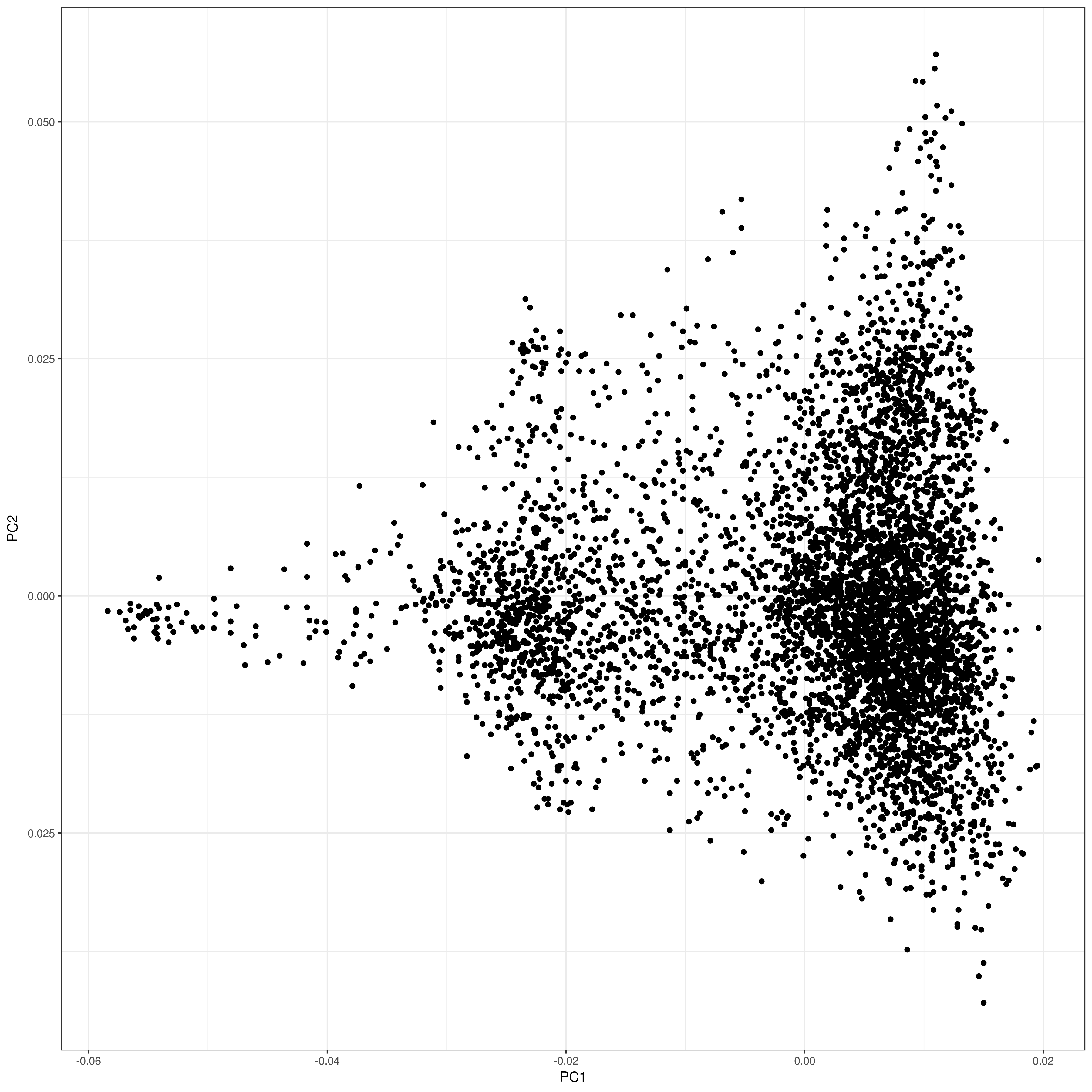
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**Figure e-5**: Single Nucleotide Polymorphisms associated with log2 levels of total cholesterol in serum. Genome-wide and suggestive significance thresholds (5e-8 and 1e-5 respectively) are indicated by the red and blue lines.

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**Figure e-6**: Scree plot of the first 10 leading components of the PCA of the PERF genotypes (N=5106)



**Figure e-7**: Plot of the two leading principal components of the PERF genotypes (N=5106)

# **Supplementary tables**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
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| **Table e-1:** Genetic associations with C1M performed on imputed genotypes. p-values below 1.3e-7, effect sizes and minor allele frequencies and nearest genes are indicated for each associated SNP. | | | | | | | | | | | | |
| CHR | BP | Minor allele | Effect size | SE | L95 | U95 | P | MAF | Nearest Gene | Rsid | Imputed position | Clump |
| 19 | 45411941 | C | -0.1619 | 0.02 | -0.1989 | -0.1248 | 1.376E-17 | 0.16 | APOE | rs429358 | Y | 1 |
| 19 | 45415713 | A | -0.169 | 0.02 | -0.209 | -0.1291 | 1.489E-16 | 0.13 | APOC1 | rs10414043 | Y | 1 |
| 19 | 45415935 | T | -0.1682 | 0.02 | -0.2082 | -0.1282 | 2.17E-16 | 0.13 | APOC1 | rs7256200 | Y | 1 |
| 19 | 45410002 | A | -0.1658 | 0.02 | -0.2059 | -0.1256 | 7.149E-16 | 0.13 | APOE | rs769449 | N | 1 |
| 19 | 45422160 | G | -0.1327 | 0.02 | -0.1674 | -0.09809 | 7.133E-14 | 0.19 | APOC1 | rs12721051 | Y | 1 |
| 19 | 45422846 | A | -0.1323 | 0.02 | -0.167 | -0.09769 | 8.437E-14 | 0.19 | APOC1 | rs56131196 | N | 1 |
| 19 | 45422946 | G | -0.1323 | 0.02 | -0.167 | -0.09769 | 8.437E-14 | 0.19 | APOC1 | rs4420638 | N | 1 |
| 19 | 45392254 | T | -0.134 | 0.02 | -0.1697 | -0.09837 | 2.074E-13 | 0.18 | PVRL2 | rs6857 | N | 1 |
| 19 | 45421254 | A | -0.1359 | 0.02 | -0.1733 | -0.09851 | 1.198E-12 | 0.16 | APOC1 | rs12721046 | Y | 1 |
| 19 | 45427125 | A | -0.1333 | 0.02 | -0.1704 | -0.09619 | 2.217E-12 | 0.16 | . | rs111789331 | Y | 1 |
| 19 | 45428234 | A | -0.1307 | 0.02 | -0.1678 | -0.09349 | 6.255E-12 | 0.16 | APOC1P1 | rs66626994 | Y | 1 |
| 19 | 45395619 | G | -0.1307 | 0.02 | -0.1684 | -0.09308 | 1.144E-11 | 0.15 | TOMM40 | rs2075650 | Y | 1 |
| 19 | 45396144 | T | -0.1307 | 0.02 | -0.1684 | -0.09308 | 1.144E-11 | 0.15 | TOMM40 | rs11556505 | Y | 1 |
| 19 | 45394336 | C | -0.1303 | 0.02 | -0.1678 | -0.0927 | 1.186E-11 | 0.16 | TOMM40 | rs71352238 | Y | 1 |
| 19 | 45395909 | G | -0.1303 | 0.02 | -0.1679 | -0.09259 | 1.372E-11 | 0.15 | TOMM40 | rs34404554 | Y | 1 |
| 19 | 45388130 | A | -0.129 | 0.02 | -0.1664 | -0.09163 | 1.481E-11 | 0.16 | PVRL2 | rs34342646 | Y | 1 |
| 19 | 45387596 | A | -0.1294 | 0.02 | -0.167 | -0.09174 | 1.815E-11 | 0.15 | PVRL2 | rs12972970 | Y | 1 |
| 19 | 45387459 | G | -0.1292 | 0.02 | -0.1669 | -0.09158 | 1.927E-11 | 0.15 | PVRL2 | rs12972156 | Y | 1 |
| 19 | 45396665 | T | -0.1017 | 0.02 | -0.1344 | -0.06904 | 1.132E-09 | 0.23 | TOMM40 | rs59007384 | N | 1 |
| 19 | 45416741 | T | -0.09688 | 0.02 | -0.1285 | -0.06521 | 2.166E-09 | 0.25 | APOC1 | rs438811 | Y | 1 |
| 19 | 45416178 | T | -0.09685 | 0.02 | -0.1285 | -0.06517 | 2.236E-09 | 0.25 | APOC1 | rs483082 | Y | 1 |
| 19 | 45418790 | C | -0.09601 | 0.02 | -0.1278 | -0.06422 | 3.461E-09 | 0.25 | APOC1 | rs5117 | Y | 1 |
| 19 | 45395844 | A | -0.123 | 0.02 | -0.1646 | -0.08136 | 7.344E-09 | 0.12 | TOMM40 | rs34095326 | Y | 2 |
| 19 | 45394969 | G | -0.09382 | 0.02 | -0.1263 | -0.06138 | 1.521E-08 | 0.23 | TOMM40 | rs184017 | Y | 1 |
| 19 | 45396219 | T | -0.09216 | 0.02 | -0.1245 | -0.05978 | 2.557E-08 | 0.23 | TOMM40 | rs157582 | N | 1 |
| 19 | 45395714 | C | -0.09212 | 0.02 | -0.1245 | -0.05974 | 2.589E-08 | 0.23 | TOMM40 | rs157581 | Y | 1 |
| 19 | 45406673 | A | -0.08464 | 0.02 | -0.1144 | -0.05488 | 2.622E-08 | 0.29 | TOMM40 | rs10119 | Y | 3 |
| 19 | 45390333 | G | -0.09128 | 0.02 | -0.1238 | -0.05878 | 3.894E-08 | 0.23 | PVRL2 | rs283815 | N | 1 |
| 1 | 159665806 | A | 0.1737 | 0.03 | 0.1106 | 0.2367 | 7.053E-08 | 0.05 | . | rs79162334 | Y | 4 |
| 1 | 159671439 | A | 0.1725 | 0.03 | 0.1094 | 0.2356 | 8.874E-08 | 0.05 | . | rs76207423 | Y | 4 |
| 1 | 159653863 | A | 0.1711 | 0.03 | 0.108 | 0.2341 | 1.079E-07 | 0.05 | . | rs16842502 | N | 4 |
| 1 | 159655792 | G | 0.1711 | 0.03 | 0.108 | 0.2341 | 1.079E-07 | 0.05 | . | rs77785080 | Y | 4 |
| 1 | 159676171 | C | 0.1718 | 0.03 | 0.1085 | 0.2352 | 1.089E-07 | 0.05 | . | rs16842559 | N | 4 |
| 1 | 159676220 | G | 0.1718 | 0.03 | 0.1085 | 0.2352 | 1.089E-07 | 0.05 | . | rs16842568 | N | 4 |
| 1 | 159681364 | C | 0.1718 | 0.03 | 0.1085 | 0.2352 | 1.089E-07 | 0.05 | . | rs3093068 | Y | 4 |
| 1 | 159697475 | C | 0.1692 | 0.03 | 0.1065 | 0.2318 | 1.256E-07 | 0.05 | . | rs16842599 | N | 4 |
| 1 | 159699031 | C | 0.1692 | 0.03 | 0.1065 | 0.2318 | 1.256E-07 | 0.05 | . | rs75056910 | N | 4 |
| 1 | 159700039 | G | 0.1692 | 0.03 | 0.1065 | 0.2318 | 1.256E-07 | 0.05 | . | rs11265260 | Y | 4 |

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| **Supplementary Table e-2:** Phenotype definition criteria | |
| **Disease** | **Criteria** |
| Hyperlipidemia | 1. Fasting serum cholesterol >7.5mm/L and/or |
|  | 1. Answered yes to having hyperlipidemia and/or |
|  | 1. E780-785 (ICD10 code) in the Danish patient registry or death registry |
| Diabetes | 1. Registered in the diabetes registry and/or |
|  | 1. Fasting serum glucose >= 7 mmol/L and/or |
|  | 1. Fasting serum HbA1c levels ≥48 mmol/mol and/or |
|  | 1. E10-E14, DO24, DH360 (ICD10 codes) in the death registry and/or |
|  | 1. Answered yes to having diabetes |
| Dementia | 1. F01-F03 G31-G32 or R54 (ICD10 code) in the Danish patient registry or death registry and/or |
|  | 1. The Short Blessed Test (SBT) ≥10 and the category fluency test with animal naming (CFT) ≤14 and/or |
|  | 1. Answered yes to having dementia |
| Alzheimer’s disease | 1. F00 + G30 (ICD10 code) in the Danish patient registry or death registry and/or |
|  | 1. Answered yes to having Alzheimer’s disease |
| Ischemic heart disease | 1. I21, 22, 24, 25 (ICD10 code) in the Danish patient registry or death registry and/or |
|  | 1. Answered yes to having ischemic heart disease |
| Peripheral arterial disease | 1. IDC10 I70.2, I73.9 (ICD10 code) in the Danish patient registry or death registry and/or |
|  | 1. Answered yes to having peripheral arterial disease |
| Congestive heart failure | 1. I50 (ICD10 code) in the Danish patient registry or death registry and/or |
|  | 1. Answered yes to having congestive heart failure |
| Cerebrovascular diseases | 1. I60-I69 (ICD10 code) in the Danish patient registry or death and/or registry |
|  | 1. Answered yes to having cerebrovascular disease |
| CVD | 1. I20-I25, I30-I52 or I60-69 (ICD10 code) in the Danish patient registry or death registry and/or |
|  | 1. Answered yes to having CVD |
| Respiratory diseases | 1. J00-J99 (ICD10 code) in the Danish patient registry or death registry and/or |
|  | 1. Answered yes to having respiratory disease |
| Digestive diseases | 1. K00-K99 (ICD10 code) in the Danish patient registry or death registry and/or |
|  | 1. Answered yes to having digestive disease |
| Genitourinary diseases | 1. N00-N99 (ICD10 code) in the Danish patient registry or death registry and/or |
|  | 1. Answered yes to having genitourinary disease |
| Musculoskeletal diseases | 1. M00-M99 (ICD10 code) in the Danish patient registry or death registry and/or |
|  | 1. Answered yes to having musculoskeletal disease |
| Neoplasms | 1. C00-C97 (except C44) or D37-48 (ICD10 code) in the Danish patient registry or death registry and/or |
|  | 1. Answered yes to having a neoplasm |

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| **Supplementary Table e-3:** APOE genotype in the study population. All available genotypes were considered (N=5106) | | | |
| Rs7412->  rs429358 | | 0 allele | 1 alleles | 2 alleles |
| 0 allele | TC/TC  E3/E3  2860 (56.0%) | TT/TC  E2/E3  675 (13.2%) | TT/TT E2/E2 37 (0.7%) |
| 1 alleles | TC/CC E3/E4 1275 (25.0%) | TT/CC E2/E4 139 (2.7%) | TT/CT (not observed) |
| 2 alleles | CC/CC E4/E4 120 (2.4%) | CT/CC (not observed) | CT/CT (not observed) |

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| **Supplementary Table e-4:** APOE allele distribution in PERF population with and without Alzheimer disease post baseline. | | |
|  | AD=0 | AD=1 |
| E2/E2 | 36  0.8% | 0  0% |
| E2/E3 | 636  13.5% | 32  10.0% |
| E2/E4 | 124  2.6% | 9  2.9% |
| E3/E3 | 2690  57.2% | 120 38.9% |
| E3/E4 | 1126  24.0% | 122  39.6% |
| E4/E4 | 92  2.0% | 25  8.1% |
|  |  |  |
| Non E4 | 3362 | 152 |
| E4 | 1342 | 156 |

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| --- | --- | --- | --- | --- |
| **Supplementary Table e-5:** PheWAS association analysis of the 38 identified markers associated to C1M. Absolute Z-scores above 1.5 are reported. | | | | |
| rsid - Nearest gene | SNP | Phenotype | Z-score | p-value |
| rs429358 APOE | 19:45411941 | Alzheimers | 9.47 | 2.70E-21 |
| rs7256200 APOC1 | 19:45415935 | Alzheimers | 9.16 | 5.01E-20 |
| rs10414043 APOC1 | 19:45415713 | Alzheimers | 9.14 | 6.43E-20 |
| rs769449 APOE | 19:45410002 | Alzheimers | 9.12 | 7.40E-20 |
| rs429358 APOE | 19:45411941 | Dementia | 8.72 | 2.84E-18 |
| rs12721051 APOC1 | 19:45422160 | Alzheimers | 8.32 | 8.59E-17 |
| rs56131196 APOC1 | 19:45422846 | Alzheimers | 8.32 | 9.16E-17 |
| rs4420638 APOC1 | 19:45422946 | Alzheimers | 8.32 | 9.16E-17 |
| rs12721046 APOC1 | 19:45421254 | Alzheimers | 8.21 | 2.19E-16 |
| rs111789331 . | 19:45427125 | Alzheimers | 8.19 | 2.62E-16 |
| rs66626994 APOC1P1 | 19:45428234 | Alzheimers | 8.13 | 4.47E-16 |
| rs12721051 APOC1 | 19:45422160 | Dementia | 7.89 | 2.98E-15 |
| rs56131196 APOC1 | 19:45422846 | Dementia | 7.88 | 3.27E-15 |
| rs4420638 APOC1 | 19:45422946 | Dementia | 7.88 | 3.27E-15 |
| rs769449 APOE | 19:45410002 | Dementia | 7.83 | 4.72E-15 |
| rs7256200 APOC1 | 19:45415935 | Dementia | 7.83 | 4.78E-15 |
| rs10414043 APOC1 | 19:45415713 | Dementia | 7.79 | 6.77E-15 |
| rs6857 PVRL2 | 19:45392254 | Alzheimers | 7.65 | 2.01E-14 |
| rs34404554 TOMM40 | 19:45395909 | Alzheimers | 7.51 | 5.71E-14 |
| rs2075650 TOMM40 | 19:45395619 | Alzheimers | 7.50 | 6.38E-14 |
| rs11556505 TOMM40 | 19:45396144 | Alzheimers | 7.50 | 6.38E-14 |
| rs12972156 PVRL2 | 19:45387459 | Alzheimers | 7.29 | 3.14E-13 |
| rs12972970 PVRL2 | 19:45387596 | Alzheimers | 7.28 | 3.34E-13 |
| rs71352238 TOMM40 | 19:45394336 | Alzheimers | 7.27 | 3.65E-13 |
| rs12721046 APOC1 | 19:45421254 | Dementia | 7.20 | 5.99E-13 |
| rs34342646 PVRL2 | 19:45388130 | Alzheimers | 7.13 | 9.94E-13 |
| rs111789331 . | 19:45427125 | Dementia | 7.12 | 1.10E-12 |
| rs66626994 APOC1P1 | 19:45428234 | Dementia | 7.10 | 1.28E-12 |
| rs59007384 TOMM40 | 19:45396665 | Alzheimers | 7.07 | 1.60E-12 |
| rs34095326 TOMM40 | 19:45395844 | Alzheimers | 6.95 | 3.70E-12 |
| rs5117 APOC1 | 19:45418790 | Alzheimers | 6.94 | 3.92E-12 |
| rs6857 PVRL2 | 19:45392254 | Dementia | 6.87 | 6.49E-12 |
| rs483082 APOC1 | 19:45416178 | Alzheimers | 6.82 | 8.80E-12 |
| rs438811 APOC1 | 19:45416741 | Alzheimers | 6.82 | 9.42E-12 |
| rs157582 TOMM40 | 19:45396219 | Alzheimers | 6.55 | 5.79E-11 |
| rs157581 TOMM40 | 19:45395714 | Alzheimers | 6.55 | 5.95E-11 |
| rs184017 TOMM40 | 19:45394969 | Alzheimers | 6.51 | 7.36E-11 |
| rs283815 PVRL2 | 19:45390333 | Alzheimers | 6.36 | 2.08E-10 |
| rs6857 PVRL2 | 19:45392254 | Hyperlipidemia | 6.32 | 2.60E-10 |
| rs34095326 TOMM40 | 19:45395844 | Hyperlipidemia | 6.32 | 2.62E-10 |
| rs34404554 TOMM40 | 19:45395909 | Hyperlipidemia | 6.19 | 5.94E-10 |
| rs2075650 TOMM40 | 19:45395619 | Hyperlipidemia | 6.17 | 6.63E-10 |
| rs11556505 TOMM40 | 19:45396144 | Hyperlipidemia | 6.17 | 6.63E-10 |
| rs71352238 TOMM40 | 19:45394336 | Hyperlipidemia | 6.01 | 1.82E-09 |
| rs34404554 TOMM40 | 19:45395909 | Dementia | 6.00 | 2.01E-09 |
| rs2075650 TOMM40 | 19:45395619 | Dementia | 5.97 | 2.31E-09 |
| rs11556505 TOMM40 | 19:45396144 | Dementia | 5.97 | 2.31E-09 |
| rs12972156 PVRL2 | 19:45387459 | Hyperlipidemia | 5.93 | 3.00E-09 |
| rs12972970 PVRL2 | 19:45387596 | Hyperlipidemia | 5.91 | 3.39E-09 |
| rs34342646 PVRL2 | 19:45388130 | Hyperlipidemia | 5.82 | 5.84E-09 |
| rs12972156 PVRL2 | 19:45387459 | Dementia | 5.73 | 9.97E-09 |
| rs12972970 PVRL2 | 19:45387596 | Dementia | 5.72 | 1.07E-08 |
| rs10119 TOMM40 | 19:45406673 | Dementia | 5.66 | 1.48E-08 |
| rs71352238 TOMM40 | 19:45394336 | Dementia | 5.62 | 1.86E-08 |
| rs429358 APOE | 19:45411941 | Hyperlipidemia | 5.55 | 2.84E-08 |
| rs59007384 TOMM40 | 19:45396665 | Dementia | 5.54 | 3.09E-08 |
| rs34342646 PVRL2 | 19:45388130 | Dementia | 5.53 | 3.26E-08 |
| rs10119 TOMM40 | 19:45406673 | Alzheimers | 5.46 | 4.89E-08 |
| rs10414043 APOC1 | 19:45415713 | Hyperlipidemia | 5.40 | 6.61E-08 |
| rs12721051 APOC1 | 19:45422160 | Hyperlipidemia | 5.39 | 7.12E-08 |
| rs56131196 APOC1 | 19:45422846 | Hyperlipidemia | 5.37 | 7.77E-08 |
| rs4420638 APOC1 | 19:45422946 | Hyperlipidemia | 5.37 | 7.77E-08 |
| rs66626994 APOC1P1 | 19:45428234 | Hyperlipidemia | 5.29 | 1.20E-07 |
| rs34095326 TOMM40 | 19:45395844 | Dementia | 5.29 | 1.21E-07 |
| rs7256200 APOC1 | 19:45415935 | Hyperlipidemia | 5.29 | 1.23E-07 |
| rs483082 APOC1 | 19:45416178 | Dementia | 5.29 | 1.24E-07 |
| rs5117 APOC1 | 19:45418790 | Dementia | 5.29 | 1.25E-07 |
| rs438811 APOC1 | 19:45416741 | Dementia | 5.27 | 1.34E-07 |
| rs111789331 . | 19:45427125 | Hyperlipidemia | 5.18 | 2.20E-07 |
| rs769449 APOE | 19:45410002 | Hyperlipidemia | 5.18 | 2.22E-07 |
| rs12721046 APOC1 | 19:45421254 | Hyperlipidemia | 5.12 | 3.04E-07 |
| rs157582 TOMM40 | 19:45396219 | Dementia | 5.07 | 3.90E-07 |
| rs157581 TOMM40 | 19:45395714 | Dementia | 5.07 | 4.04E-07 |
| rs184017 TOMM40 | 19:45394969 | Dementia | 4.93 | 8.19E-07 |
| rs283815 PVRL2 | 19:45390333 | Dementia | 4.90 | 9.67E-07 |
| rs10119 TOMM40 | 19:45406673 | Hyperlipidemia | 3.65 | 2.58E-04 |
| rs429358 APOE | 19:45411941 | Neoplasms | -3.65 | 2.65E-04 |
| rs6857 PVRL2 | 19:45392254 | Neoplasms | -3.36 | 7.90E-04 |
| rs157582 TOMM40 | 19:45396219 | Hyperlipidemia | 3.19 | 1.43E-03 |
| rs283815 PVRL2 | 19:45390333 | Hyperlipidemia | 3.15 | 1.66E-03 |
| rs157581 TOMM40 | 19:45395714 | Hyperlipidemia | 3.14 | 1.71E-03 |
| rs184017 TOMM40 | 19:45394969 | Hyperlipidemia | 3.13 | 1.73E-03 |
| rs59007384 TOMM40 | 19:45396665 | Hyperlipidemia | 3.06 | 2.20E-03 |
| rs769449 APOE | 19:45410002 | Neoplasms | -3.05 | 2.29E-03 |
| rs56131196 APOC1 | 19:45422846 | Neoplasms | -3.03 | 2.46E-03 |
| rs4420638 APOC1 | 19:45422946 | Neoplasms | -3.03 | 2.46E-03 |
| rs12721051 APOC1 | 19:45422160 | Neoplasms | -3.01 | 2.60E-03 |
| rs7256200 APOC1 | 19:45415935 | Neoplasms | -2.85 | 4.42E-03 |
| rs10414043 APOC1 | 19:45415713 | Neoplasms | -2.81 | 5.02E-03 |
| rs184017 TOMM40 | 19:45394969 | Neoplasms | -2.80 | 5.15E-03 |
| rs157581 TOMM40 | 19:45395714 | Neoplasms | -2.79 | 5.21E-03 |
| rs71352238 TOMM40 | 19:45394336 | Neoplasms | -2.78 | 5.48E-03 |
| rs283815 PVRL2 | 19:45390333 | Neoplasms | -2.74 | 6.10E-03 |
| rs157582 TOMM40 | 19:45396219 | Neoplasms | -2.74 | 6.14E-03 |
| rs2075650 TOMM40 | 19:45395619 | Neoplasms | -2.70 | 7.04E-03 |
| rs11556505 TOMM40 | 19:45396144 | Neoplasms | -2.70 | 7.04E-03 |
| rs34404554 TOMM40 | 19:45395909 | Neoplasms | -2.68 | 7.46E-03 |
| rs34342646 PVRL2 | 19:45388130 | Neoplasms | -2.62 | 8.76E-03 |
| rs59007384 TOMM40 | 19:45396665 | Neoplasms | -2.53 | 1.15E-02 |
| rs12972970 PVRL2 | 19:45387596 | Neoplasms | -2.50 | 1.24E-02 |
| rs12972156 PVRL2 | 19:45387459 | Neoplasms | -2.48 | 1.31E-02 |
| rs483082 APOC1 | 19:45416178 | Neoplasms | -2.41 | 1.59E-02 |
| rs5117 APOC1 | 19:45418790 | Neoplasms | -2.40 | 1.63E-02 |
| rs438811 APOC1 | 19:45416741 | Neoplasms | -2.39 | 1.69E-02 |
| rs5117 APOC1 | 19:45418790 | Genitourinary.diseases | 2.28 | 2.26E-02 |
| rs483082 APOC1 | 19:45416178 | Genitourinary.diseases | 2.26 | 2.36E-02 |
| rs438811 APOC1 | 19:45416741 | Genitourinary.diseases | 2.25 | 2.47E-02 |
| rs12721046 APOC1 | 19:45421254 | Neoplasms | -2.17 | 3.01E-02 |
| rs66626994 APOC1P1 | 19:45428234 | Neoplasms | -2.14 | 3.20E-02 |
| rs111789331 . | 19:45427125 | Neoplasms | -2.13 | 3.32E-02 |
| rs12721051 APOC1 | 19:45422160 | Genitourinary.diseases | 2.05 | 4.01E-02 |
| rs429358 APOE | 19:45411941 | CVD | -2.05 | 4.06E-02 |
| rs56131196 APOC1 | 19:45422846 | Genitourinary.diseases | 2.02 | 4.33E-02 |
| rs4420638 APOC1 | 19:45422946 | Genitourinary.diseases | 2.02 | 4.33E-02 |
| rs34342646 PVRL2 | 19:45388130 | Peripheral.arterial.disease | 2.01 | 4.49E-02 |
| rs10119 TOMM40 | 19:45406673 | Genitourinary.diseases | 1.94 | 5.30E-02 |
| rs10414043 APOC1 | 19:45415713 | CVD | -1.93 | 5.35E-02 |
| rs6857 PVRL2 | 19:45392254 | CVD | -1.91 | 5.57E-02 |
| rs56131196 APOC1 | 19:45422846 | CVD | -1.90 | 5.68E-02 |
| rs4420638 APOC1 | 19:45422946 | CVD | -1.90 | 5.68E-02 |
| rs66626994 APOC1P1 | 19:45428234 | CVD | -1.90 | 5.72E-02 |
| rs7256200 APOC1 | 19:45415935 | CVD | -1.88 | 5.94E-02 |
| rs12721046 APOC1 | 19:45421254 | CVD | -1.88 | 6.07E-02 |
| rs12972156 PVRL2 | 19:45387459 | Peripheral.arterial.disease | 1.88 | 6.08E-02 |
| rs12721051 APOC1 | 19:45422160 | CVD | -1.87 | 6.15E-02 |
| rs6857 PVRL2 | 19:45392254 | Genitourinary.diseases | 1.87 | 6.22E-02 |
| rs12972970 PVRL2 | 19:45387596 | Peripheral.arterial.disease | 1.86 | 6.23E-02 |
| rs111789331 . | 19:45427125 | CVD | -1.85 | 6.49E-02 |
| rs34404554 TOMM40 | 19:45395909 | Peripheral.arterial.disease | 1.82 | 6.82E-02 |
| rs769449 APOE | 19:45410002 | CVD | -1.82 | 6.92E-02 |
| rs2075650 TOMM40 | 19:45395619 | Peripheral.arterial.disease | 1.81 | 7.05E-02 |
| rs11556505 TOMM40 | 19:45396144 | Peripheral.arterial.disease | 1.81 | 7.05E-02 |
| rs34095326 TOMM40 | 19:45395844 | CVD | -1.77 | 7.59E-02 |
| rs429358 APOE | 19:45411941 | Genitourinary.diseases | 1.76 | 7.87E-02 |
| rs71352238 TOMM40 | 19:45394336 | Peripheral.arterial.disease | 1.74 | 8.16E-02 |
| rs59007384 TOMM40 | 19:45396665 | Genitourinary.diseases | 1.71 | 8.74E-02 |
| rs16842599 . | 1:159697475 | CVD | 1.68 | 9.37E-02 |
| rs75056910 . | 1:159699031 | CVD | 1.68 | 9.37E-02 |
| rs11265260 . | 1:159700039 | CVD | 1.68 | 9.37E-02 |
| rs59007384 TOMM40 | 19:45396665 | CVD | -1.67 | 9.44E-02 |
| rs16842502 . | 1:159653863 | Alzheimers | -1.66 | 9.63E-02 |
| rs77785080 . | 1:159655792 | Alzheimers | -1.66 | 9.63E-02 |
| rs79162334 . | 1:159665806 | Alzheimers | -1.66 | 9.70E-02 |
| rs184017 TOMM40 | 19:45394969 | CVD | -1.66 | 9.75E-02 |
| rs111789331 . | 19:45427125 | Peripheral.arterial.disease | 1.65 | 9.83E-02 |
| rs76207423 . | 1:159671439 | Alzheimers | -1.65 | 9.84E-02 |
| rs16842559 . | 1:159676171 | Alzheimers | -1.64 | 1.00E-01 |
| rs16842568 . | 1:159676220 | Alzheimers | -1.64 | 1.00E-01 |
| rs3093068 . | 1:159681364 | Alzheimers | -1.64 | 1.00E-01 |
| rs10119 TOMM40 | 19:45406673 | Musculoskeletal.diseases | -1.64 | 1.01E-01 |
| rs34095326 TOMM40 | 19:45395844 | Musculoskeletal.diseases | -1.64 | 1.02E-01 |
| rs16842599 . | 1:159697475 | Alzheimers | -1.63 | 1.02E-01 |
| rs75056910 . | 1:159699031 | Alzheimers | -1.63 | 1.02E-01 |
| rs11265260 . | 1:159700039 | Alzheimers | -1.63 | 1.02E-01 |
| rs157581 TOMM40 | 19:45395714 | CVD | -1.63 | 1.03E-01 |
| rs66626994 APOC1P1 | 19:45428234 | Peripheral.arterial.disease | 1.62 | 1.05E-01 |
| rs12972156 PVRL2 | 19:45387459 | CVD | -1.62 | 1.06E-01 |
| rs12972970 PVRL2 | 19:45387596 | CVD | -1.60 | 1.10E-01 |
| rs34404554 TOMM40 | 19:45395909 | CVD | -1.59 | 1.13E-01 |
| rs12721046 APOC1 | 19:45421254 | Digestive.diseases | -1.58 | 1.14E-01 |
| rs157582 TOMM40 | 19:45396219 | CVD | -1.58 | 1.14E-01 |
| rs283815 PVRL2 | 19:45390333 | CVD | -1.58 | 1.15E-01 |
| rs2075650 TOMM40 | 19:45395619 | CVD | -1.57 | 1.17E-01 |
| rs11556505 TOMM40 | 19:45396144 | CVD | -1.57 | 1.17E-01 |
| rs12972156 PVRL2 | 19:45387459 | Musculoskeletal.diseases | -1.56 | 1.19E-01 |
| rs12972970 PVRL2 | 19:45387596 | Musculoskeletal.diseases | -1.55 | 1.22E-01 |
| rs483082 APOC1 | 19:45416178 | Cerebrovascular.diseases | 1.55 | 1.22E-01 |
| rs157582 TOMM40 | 19:45396219 | Genitourinary.diseases | 1.53 | 1.25E-01 |
| rs34342646 PVRL2 | 19:45388130 | Musculoskeletal.diseases | -1.53 | 1.26E-01 |
| rs5117 APOC1 | 19:45418790 | Cerebrovascular.diseases | 1.53 | 1.27E-01 |
| rs438811 APOC1 | 19:45416741 | Cerebrovascular.diseases | 1.52 | 1.27E-01 |
| rs71352238 TOMM40 | 19:45394336 | CVD | -1.51 | 1.31E-01 |
| rs34342646 PVRL2 | 19:45388130 | CVD | -1.51 | 1.31E-01 |
| rs34095326 TOMM40 | 19:45395844 | Neoplasms | -1.50 | 1.33E-01 |

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| --- | --- | --- | --- | --- | --- |
| **Supplementary Table e-6:** Pathway enrichment analysis performed on genetic associations with C1M. | | | | | |
| Pathway | N Genes Mapped | N Genes Used | N Samples | Empirical P | Genes |
| 511721 GO:0050750 low-density lipoprotein particle receptor binding | 14 | 14 | 1000000 | 1,40E-05 | LDLRAP1, PCSK9, CRP, APOB, LANCL1, AP2M1, LRPAP1, MMP13, APOA5, SYT1, HSP90B1, SLC9A3R2, ARRB2, APOE |
| 515258 GO:0070325 lipoprotein particle receptor binding | 18 | 16 | 500000 | 4,80E-05 | LDLRAP1, PCSK9, CRP, APOB, LANCL1, AP2M1, LRPAP1, RELN, MMP13, APOA1, LRP1, SYT1, HSP90B1, SLC9A3R2, ARRB2, APOE |
| 519122 GO:2000482 regulation of interleukin-8 secretion | 14 | 12 | 100000 | 2,70E-04 | PTPN22, CD2, CRP, CD244, ANXA4, WNT5A, F2RL1, ANXA1, NLRP10, LGALS9, FFAR2, SSC5D |
| 511933 GO:0051000 positive regulation of nitric-oxide synthase activity | 17 | 17 | 100000 | 3,10E-04 | NOS1AP, HTR2B, TERT, NPR3, DHFR, ESR1, NOD1, PTK2B, KRAS, SCARB1, GCH1, CALM1, AKT1, TERF2, FCER2, APOE, CALM3 |
| 501996 GO:0032770 positive regulation of monooxygenase activity | 24 | 24 | 100000 | 3,60E-04 | PARK7, NOS1AP, IL1B, HTR2B, TERT, NPR3, GDNF, DHFR, TNF, ESR1, NOD1, POR, PTK2B, KRAS, IFNG, SCARB1, GCH1, CALM1, AKT1, CDH3, TERF2, FCER2, APOE, CALM3 |
| 516736 GO:0071814 protein-lipid complex binding | 21 | 20 | 100000 | 4,00E-04 | LRP8, PCSK9, CRP, STAB1, CD36, MSR1, VLDLR, APOA1, SORL1, STAB2, SCARB1, THBS1, LIPC, CDH13, SCARF1, MAPT, COLEC12, LDLR, APOE, APOL2 |
| 492412 GO:0071813 lipoprotein particle binding | 21 | 20 | 100000 | 4,70E-04 | LRP8, PCSK9, CRP, STAB1, CD36, MSR1, VLDLR, APOA1, SORL1, STAB2, SCARB1, THBS1, LIPC, CDH13, SCARF1, MAPT, COLEC12, LDLR, APOE, APOL2 |
| 513958 GO:0060402 calcium ion transport into cytosol | 39 | 39 | 100000 | 4,70E-04 | XCL1, PTPRC, ATP2B4, RYR2, SLC8A1, PRKCE, HTR2B, ITPR1, PKD2, FGF2, F2R, ITPR3, IBTK, TRDN, ADRA1A, TRPA1, JPH1, TPCN2, DRD2, ITPR2, TPCN1, P2RX7, HTR2A, RASA3, JPH4, ERO1A, SLC8A3, TRPM1, RYR3, NOL3, PLCG2, JPH3, TRPV1, CCR7, MCOLN1, CHERP, RYR1, FKBP1A, JPH2 |
| 507890 GO:0045540 regulation of cholesterol biosynthetic process | 12 | 12 | 100000 | 5,00E-04 | APOB, SCAP, PRKAA1, FGF1, POR, PEX2, ERLIN1, SREBF1, APOE, SOD1, ABCG1, SEC14L2 |
| 1269246 R-HSA-173623 Classical antibody-mediated complement activation | 5 | 3 | 100000 | 5,10E-04 | C1QB, CRP, C1R |
| 503576 GO:0034374 low-density lipoprotein particle remodeling | 9 | 9 | 50000 | 5,60E-04 | PLA2G2A, AGT, APOB, AGTR1, PLA2G7, LIPC, CETP, APOE, ABCG1 |
| 512105 GO:0051209 release of sequestered calcium ion into cytosol | 32 | 32 | 50000 | 5,80E-04 | XCL1, PTPRC, RYR2, PRKCE, HTR2B, ITPR1, PKD2, FGF2, F2R, ITPR3, IBTK, TRDN, TRPA1, TPCN2, DRD2, ITPR2, TPCN1, P2RX7, HTR2A, RASA3, ERO1A, RYR3, NOL3, PLCG2, JPH3, TRPV1, CCR7, MCOLN1, CHERP, RYR1, FKBP1A, JPH2 |
| 512169 GO:0051283 negative regulation of sequestering of calcium ion | 32 | 32 | 50000 | 6,20E-04 | XCL1, PTPRC, RYR2, PRKCE, HTR2B, ITPR1, PKD2, FGF2, F2R, ITPR3, IBTK, TRDN, TRPA1, TPCN2, DRD2, ITPR2, TPCN1, P2RX7, HTR2A, RASA3, ERO1A, RYR3, NOL3, PLCG2, JPH3, TRPV1, CCR7, MCOLN1, CHERP, RYR1, FKBP1A, JPH2 |
| 513957 GO:0060401 cytosolic calcium ion transport | 40 | 40 | 50000 | 6,60E-04 | XCL1, PTPRC, ATP2B4, RYR2, SLC8A1, PRKCE, HTR2B, ITPR1, PKD2, FGF2, F2R, ITPR3, IBTK, TRDN, ADRA1A, TRPA1, JPH1, TPCN2, DRD2, ITPR2, ATP2A2, TPCN1, P2RX7, HTR2A, RASA3, JPH4, ERO1A, SLC8A3, TRPM1, RYR3, NOL3, PLCG2, JPH3, TRPV1, CCR7, MCOLN1, CHERP, RYR1, FKBP1A, JPH2 |
| 503579 GO:0034377 plasma lipoprotein particle assembly | 14 | 11 | 50000 | 6,80E-04 | SOAT1, APOB, ACSL3, MTTP, APOM, ABCA1, APOA1, SOAT2, FECH, ABCA7, APOE |
| 510293 GO:0048168 regulation of neuronal synaptic plasticity | 44 | 44 | 50000 | 8,20E-04 | EPHB2, BCAN, KCNJ10, CNTN2, AGT, RAB3GAP1, GSK3B, KIT, SNCA, CAMK2A, DRD1, DBN1, SYNGAP1, RIMS1, GRIK2, CAMK2B, UNC13B, GRIN1, EGR2, NEURL1, HRAS, GRM5, DRD2, KMT2A, KRAS, RAB11A, NPTN, RASGRF1, SHISA9, JPH3, DLG4, SHISA6, NF1, NETO1, RAB8A, UNC13A, RAB3A, APOE, SLC8A2, PPFIA3, SHISA7, S100B, SYNGR1, SHANK3 |
| 946901 GO:1902656 calcium ion import into cytosol | 33 | 33 | 50000 | 8,60E-04 | XCL1, PTPRC, ATP2B4, RYR2, PRKCE, HTR2B, ITPR1, PKD2, FGF2, F2R, ITPR3, IBTK, TRDN, TRPA1, TPCN2, DRD2, ITPR2, TPCN1, P2RX7, HTR2A, RASA3, ERO1A, RYR3, NOL3, PLCG2, JPH3, TRPV1, CCR7, MCOLN1, CHERP, RYR1, FKBP1A, JPH2 |
| 511969 GO:0051044 positive regulation of membrane protein ectodomain proteolysis | 14 | 14 | 50000 | 9,60E-04 | TNFRSF1B, NRDC, IL1B, SH3D19, GPLD1, TNF, SNX9, ADAM9, ADRA2A, ADAM8, IFNG, SNX33, FURIN, APOE |

# **Supplementary methods**

### Genotyping and imputation

Out of 5553 DNA samples collected, 5516 have been genotyped successfully. Genotyping of 5516 PERF study baseline participants was performed on the collected DNA samples using a custom-made Illumina Global Screening Array version 2 (693143 probes) in collaboration with deCODE Genetics, Iceland. The probe annotation of this panel was in GRCh38 reference.

SNP Imputation was performed in two steps by first curating the genotype array files, mapped to the original GRCh37 annotation of the SNP array and correcting strand flips using HRC-1000G-check-bim-v4.2.10 [1], GenGen-1.0.1 [2] and checkvcf [3]. We then submitted the genotypes to the Michigan Imputation Server [4] https://imputationserver.sph.umich.edu/index.html#! , run date 2019-05-29. The reference panel used for this step is the HRC r1.1.2016, EUR population. Phasing was performed with ShapeIt2 and the imputation with Minimac3. SNP identifiers of variants in the HRC panels have been mapped to Entrez gene identifiers using the flat file available at ftp://ftp.ncbi.nih.gov/snp/redesign/pre\_build152/Entrez/eLinks/snp\_genes.gz . Conversion to HGNC symbols was performed using the ensembl97 GRCh37 reference.

### Functional enrichment analysis

Pathway enrichment analysis has been performed on GWAS results obtained from the non-imputed SNP position, using the tool Vegas2v2 [5], using the default 0k window and the provided hg19 and Biosystems gene-pathway annotation files provided by the Vegas tool website. Associations with an empirical P less or equal to 0.001 are reported in Supplementary Table S6.

# **References**

[1] HRC-1000G check-bim tool: https://github.com/eauforest/imputePrepSanger/blob/master/

[2] Gengen toolbox: http://gengen.openbioinformatics.org/en/latest/

[3] checkVCF tool: https://github.com/zhanxw/checkVCF

[4] Das S, Forer L, Schönherr S, Sidore C, Locke AE, Kwong A, Vrieze S, Chew EY, Levy S, McGue M, Schlessinger D, Stambolian D, Loh PR, Iacono WG, Swaroop A, Scott LJ, Cucca F, Kronenberg F, Boehnke M, Abecasis GR, Fuchsberger C. Next-generation genotype imputation service and methods. Nature Genetics 48, 1284–1287 (2016).

[5] Mishra A, Macgregor S. VEGAS2: Software for More Flexible Gene-Based Testing. *Twin Research and Human Genetics*,86-91 (2015).