A. Supplemental Material. InCHIANTI Frailty Analysis and Biomarkers

Model generation

The predictive genetic and laboratory biomarkers were identified in a comprehensive systematic review and analyzed using an Extreme Gradient Boosting (xgboost) in R14. While boosting was initially developed for machine learning, ‘xgboost’ in R is based in boosted trees. Xgboost is an open source tool and a variant of the gradient boosting machine and uses a tree based model. Xgboost is used in this study for a supervised learning problem where the variables identified from the systematic review are used to predict, pre-frail and frail individuals.

Evaluation of the model

With the use of any predictive model in machine learning there is a chance for inflated risk of capitalizing on chance features (overfitting) in the data. Overfitting of the integrative model was mitigated in two ways: 1) having a distinct training and validation process for the model and 2) using xgb in R which has a built-in parameter settings for selection to reduce poor predictive performance. *Internal validation:* A randomly assigned training subset was used to validate the model within the InCHIANTI cohort *in silico* (via simulation).

Calibration of the model

Parameter estimates for each predictive factor and associated descriptive statistics was evaluated to provide biological insight into the underpinnings of the classification algorithm. We first evaluated the calibration by partitioning the data into 5, 10, 20, 30, 40, 50, 75, 100 and 200 groups and then ran the calibration test. Next, we repeated tests for all possible values between 5-200 groups and evaluated the distribution of the test statistic. The best prediction thresholds were determined using AUC, 93.8%.

Genetic Data

Genotypic data was generated at the National Institute on Aging’s Laboratory of Neurogenics. Samples of genomic DNA extracted from leukocytes17. Genotypic data used for the model were extracted out of the binary Plink files from the InCHIANTI database. SNPs which could not be identified in the binary files were extracted from genotype imputed files, genotype imputation was completed with Minimac (V2). The SNPs included meet the following standard: per variant and per sample missingness < 5%, European ancestry, MAF < 0.001 and a rsq < 0.3. Additionally, Samples were filtered for 95% or greater genotyping call rate, no ancestry outliers, and no sex discrepancies.

Demographic Data

Demographic data included gender, age, and level of education. Disease processes considered as confounders included baseline diagnosis of: baseline dementia (n=82), vascular dementia (n=41), depression (n=412), and Parkinson’s disease (n=16).

**Supplementary Data Table I: Laboratory values as they appear in the InCHIANTI** **Datasets by Clinical Category**

|  |  |  |
| --- | --- | --- |
| **Inflammatory/Immunity** | **Nutrient Biomarker** | **Lipid Metabolism** |
| BL Uric acid (mg/dL) | BL Omega-3 fatty acids as % of total fatty acid area | BL Lipids: total cholesterol (mg/dL) |
| BL Urinary cortisol (µg/mL) | BL Omega-3 plasma fatty acid weight (mg/L) | BL Lipids: HDL cholesterol (mg/dL) |
| BL 24-hour urinary cortisol (µg/24 hours) | BL Omega-3 fatty acids as % of total fatty acid weight | BL Lipids: triglycerides (mg/dL) |
| BL C-reactive protein - low sensitivity (µg/mL) | BL Omega-3 fatty acids as % of total fatty acid mols | BL Lipids: LDL cholesterol (mg/dL) |
| BL C-reactive protein - high sensitivity (µg/mL) | BL Omega-6 fatty acids as % of total fatty acid area | BL Lipoprotein(a) (mg/dL) |
| BL Interleukin-6 via ELISA ultrasensitive (pg/mL) | BL Omega-6 plasma fatty acid weight (mg/L) |  |
| BL IL-6 high-sensitivity ELISA calculated from ELISA ultrasensitive (pg/mL) | BL Omega-6 fatty acids as % of total fatty acid weight | **Metabolomics(plasma lipids)** |
| BL Soluble IL-6 receptor via ELISA (ng/mL) | BL Omega-6 fatty acids as % of total fatty acid mols | BL Fatty acid C16:0 (palmitiA91:A116c) area |
| BL Interleukin-10 via ELISA (pg/mL) | BL Ratio of Omega-6:Omega-3 as % of total fatty acid area | BL Fatty acid C16:0 (palmitic) area |
| BL Interleukin-1 receptor antagonist via ELISA ultrasensitive (pg/mL) | BL Ratio of Omega-6:Omega-3 as % of total fatty acid weight | BL Fatty acid C16:0 as % of total fatty acid area |
| BL Interleukin-1B via ELISA (pg/mL) | BL Ratio of Omega-6:Omega-3 as % of total fatty acid mols | BL Fatty acid C16:0 weight (mg/L) |
| BL Interleukin-18 via ELISA ultrasensitive using plasma (pg/mL) | BL Vitamin B6 via high performance liquid chromatography (ng/mL) | BL Fatty acid C16:0 as % of total fatty acid weight |
| BL Transforming growth factor-B1 (pg/mL) | BL Vitamin B6 via high performance liquid chromatography (nmol/L) | BL Fatty acid C16:0 (µmol/L) |
| BL Tumor necrosis factor-a via multiplex technology (pg/mL) | BL Vitamin E gamma tocopherol, high performance liquid chromatography (µmol/L) | BL Fatty acid C16:0 as % of total fatty acid mols |
| BL Soluble TNF-a receptor I via quantitative sandwich EIA (pg/mL) | BL Vitamin E alpha tocopherol, high performance liquid chromatography (µmol/L) | BL Fatty acid C20:0 (arachidic) area |
| BL Soluble TNF-a receptor II via quantitative sandwich EIA (pg/mL) | BL Vitamin E gamma tocopherol, high performance liquid chromatography, assay #2 (µmol/L) | BL Fatty acid C20:0 as % of total fatty acid area |
| BL TNF-related apoptosis-inducing ligand (pg/mL) | BL Vitamin E alpha tocopherol, high performance liquid chromatography, assay #2 (µmol/L) | BL Fatty acid C20:0 weight (mg/L) |
| BL Interleukin-8 via Bio-Plex (pg/mL) | BL Beta-carotene via high performance liquid chromatography (µmol/L) | BL Fatty acid C20:0 as % of total fatty acid weight |
| BL Interleukin-12 via Bio-Plex (pg/mL) | BL Lycopene via high performance liquid chromatography (µmol/L) | BL Fatty acid C20:0 (µmol/L) |
| BL Monocyte chemoattractant protein-1 via Bio-Plex (pg/mL) | BL Total proteins (g/dL) | BL Fatty acid C20:0 as % of total fatty acid mols |
| BL Macrophage inflammatory protein-1b via Bio-Plex (pg/mL) | BL Albumin (%) | BL Fatty acid C20:5 n-3 cis (eicosapentaenoic, EPA) area |
| BL Serum cortisol (µg/dL) |  | BL Fatty acid C20:5 n-3 as % of total fatty acid area |
| BL Serum cortisol (nmol/L) |  | BL Fatty acid C20:5 n-3 weight (mg/L) |
| BL Dehydroepiandrosterone sulfate (µg/dL) |  | BL Fatty acid C20:5 n-3 as % of total fatty acid weight |
| BL Dehydroepiandrosterone sulfate (nmol/L) |  | BL Fatty acid C20:5 n-3 (µmol/L) |
| BL Cortisol:DHEAS ratio (based on nmols) |  | BL Fatty acid C20:5 n-3 as % of total fatty acid mols |
| BL Soluble CD14 via ELISA (ng/mL) |  | BL Fatty acid C22:0 (behenic) area |
| BL Fibrinogen (mg/dL) |  | BL Fatty acid C22:0 as % of total fatty acid area |
| BL Erythrocyte sedimentation rate (ESR) (mm/hour) |  | BL Fatty acid C22:0 weight (mg/L) |
| BL Homocysteine via FPIA analysis (µmol/L) |  | BL Fatty acid C22:0 as % of total fatty acid weight |
| BL Resistin via EIA (ng/mL)- |  | BL Fatty acid C22:0 (µmol/L) |
| BL Adiponectin via RIA (µg/mL)-(metabolic function) |  | BL Fatty acid C22:0 as % of total fatty acid mols |
| BL Advanced glycation endproduct (AGE): Carboxymethyl-lysine (ng/mL) |  | BL Fatty acid C24:0 (lignoceric) area |
| BL Alpha-1 globulin (%) |  | BL Fatty acid C24:0 as % of total fatty acid area |
| BL Alpha-2 globulin (%) |  | BL Fatty acid C24:0 weight (mg/L) |
| BL Alpha-2-macroglobulin (mg/dL) |  | BL Fatty acid C24:0 as % of total fatty acid weight |
| BL Beta globulins (%) |  | BL Fatty acid C24:0 (µmol/L) |
| BL Endogenous secretory receptor for AGEs (ng/mL) |  | BL Fatty acid C24:0 as % of total fatty acid mols |
| **Renal/Electrolyte** | **Hematology/Liver** | **Endocrine/Hormones** |
| BL Na+ (mEq/L) | BL White blood cells (WBC) (n, K/µL) | BL Blood glucose (mg/dL) |
| BL Ca++ (mg/dL) | BL Neutrophils (n, K/µL) | BL 25(OH)-D (25-hydroxyvitamin D) via RIA (nmol/L) |
| BL Urinary creatinine (mg/dL) | BL Lymphocytes (n, K/µL) | BL Parathyroid hormone, two-site immunoradiometric assay (pg/mL) |
| BL 24-hour urinary creatinine (mg/24 hours) | BL Monocytes (n, K/µL) | BL Thyroid stimulating hormone, TSH (mIU/L) |
| BL Creatinine clearance, 24-hr urine (mL/minute) | BL Neutrophils (%) | BL Free thyroxine, fT4 (ng/dL) |
| BL Urinary Ca (mmol/L) | BL Lymphocytes (%) | BL Plasma insulin via RIA (mIU/L) |
| BL Urinary Na (mmol/L) | BL Monocytes (%) | BL Total testosterone (ng/mL) |
| BL Urine glucose (mg/dL) | BL Red blood cells (RBC) (n, millions/µL) | BL Total testosterone (nmol/L) |
| BL Urine proteins (mg/dL) | BL Hemoglobin (g/dL) | BL Free testosterone (ng/dL), Vermeulen |
| BL Urine hemoglobin (mg/dL) | BL Hematocrit (%) | BL Free testosterone (nmol/L), Vermeulen |
| BL Urine ketones (mg/dL) | BL Mean corpuscular volume (MCV) (fL) | BL Estradiol via radioimmunoassay (pg/mL) |
| BL Urine bilirubin (mg/dL) | BL Mean corpuscular hemoglobin (MCH) (pg) | BL Estradiol via radioimmunoassay (nmol/L) |
| BL Urine urobilinogen (mg/dL) | BL MCH concentration (MCHC) (g/dL) | BL C-terminal telopeptide of type-1 collagen (ng/mL) |
| BL Urine nitrites | BL Red cell distribution width (RDW) (%) | BL Total insulin-like growth factor-1, serum, immunoradiometric assay (ng/mL)-(IGFBP1) |
| BL Serum creatinine (mg/dL) | BL Mean platelet volume (MPV) (fL) | BL IGF binding protein-3, serum, immunoradiometric assay (ng/mL) \*\*\*corrected\*\*\* |
| BL Blood urea nitrogen (mg/dL) | BL Ferritin (ng/mL) | BL IGF binding protein-3, serum, immunoradiometric assay (nmol/L) |
| BL Creatine phosphokinase (U/L) | BL Folate via RIA (ng/mL) |  |
| BL Cystatin C (mg/L) | BL Folate via RIA (nmol/L) |  |
|  | BL Vitamin B12 via RIA (pg/mL) |  |
|  | BL Vitamin B12 via RIA (pmol/L) |  |
|  | BL Methylmalonic acid(methylmalonic aciduria), MMA (µmol/L) |  |
|  | BL Soluble transferrin receptor (nmol/L) |  |
|  | BL Soluble transferrin receptor (mg/L) |  |
|  | BL GOT (also known as AST) (U/L) |  |
|  | BL GPT (also known as ALT) (U/L) |  |
|  | BL Gamma glutamyl transferase (U/L) |  |
|  | BL Retinol via high performance liquid chromatography (µmol/L) |  |

**Supplementary Data Table II: Variants included in the Genomic Risk Score GRS calculations and individual effect estimates of single variates for predictive modeling. Phenotype association is based on the findings from the systematic review and the relationship found between variant and disease outcome.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variant Name-Allele | Allele Frequency  (%) | Gene/Closest RefSeq Gene | Variant Detail-dbSNP | Phenotype Association |
| rs1048945\_C | 1.3 | APEX1 | rs1048945 C/G Ancestral: G Minor: C | Cognition |
| rs1052133\_G | 20.6 | OGG1 | rs1052133 C/G Ancestral: C Minor: G | Cognition |
| rs1064039\_T | 19.0 | CST3 | rs1064039 A/G Ancestral: G Minor: T | Cognition |
| rs10793294\_C | 21.7 | GAB2 | rs10793294 A/C Ancestral: G Minor: C | Cognition |
| rs10883631\_G | 48.4 | BTRC | rs10883631 A/G Ancestral: G Minor: A | Frail |
| rs10883642\_G | 48.4 | BTRC | rs10883642 A/G Ancestral: A Minor: A | Frail |
| rs11225434\_C | 47.9 | WTAPP1 | rs11225434 C/T Ancestral: T Minor: C | Cognition |
| rs113263161\_A | 10.4 | **CCRL2**/LOC102724297 | rs113263161 A/G Ancestral: G Minor: A | Cognition |
| rs1133174\_A | 41.0 | SORL1 | rs1133174 A/G Ancestral: G Minor: A | Cognition |
| rs11574428\_A | 10.2 | CCRL2 | rs11574428 A/T Ancestral: T Minor: A | Cognition |
| rs11575821\_A | 11.4 | **CCRL2**/LOC102724297 | rs11575821 A/G Ancestral: G Minor: A | Cognition |
| rs1207568\_A | 19.4 | KLOTHO | rs1207568 C/T Ancestral: C Minor: A | Cognition |
| rs13113697\_T | 27.2 | **HS3ST1**/LOC107986178 | rs13113697 G/T Ancestral: G Minor: T | Cognition |
| rs1468063\_T | 12.4 | FAS | rs1468063 A/G Ancestral: G Minor: T | Cognition |
| rs1566728\_C | 14.1 | PTPRJ | rs1566728 A/G Ancestral: G Minor: C | Frail |
| rs16944\_A | 33.4 | IL1B | rs16944 A/G Ancestral: A Minor: A | Cognition |
| rs1799990\_G | 30.9 | PRNP | rs1799990 A/G Ancestral: A Minor: G | Cognition |
| rs1800629\_A | 12.3 | TNF | rs1800629 A/G Ancestral: G Minor: A | Cog/Frail |
| rs1800764\_C | 47.6 | ACE | rs1800764 C/T Ancestral: C Minor: T | Cognition |
| rs1800796\_C | 5.0 | IL6 | rs1800796 C/G Ancestral: G Minor: C | Cog/Frail |
| rs1801394\_G | 43.9 | MTRR | rs1801394 A/G Ancestral: A Minor: G | Frail |
| rs2047812\_A | 14.8 | PTPRJ | rs2047812 C/T Ancestral: C Minor: A | Frail |
| rs2227729\_G | 7.5 | VTN | rs2227729 C/T Ancestral: C Minor: G | Frail |
| rs2228145\_C | 38.0 | IL6-R | rs2228145 A/C/T Ancestral: A Minor: C | Cognition |
| rs2228467\_C | 8.2 | CCL4 | rs2228467 C/T Ancestral: T Minor: C | Cognition |
| rs2229238\_T | 16.9 | IL6-R | rs2229238 C/T Ancestral: C Minor: T | Cognition |
| rs2267163\_T | 36.5 | TCN2 | rs2267163 C/T Ancestral: C Minor: T | Frail |
| rs2283368\_C | 12.3 | KLOTHO | rs2283368 C/T Ancestral: T Minor: C | Cognition |
| rs2465481\_A | 47.0 | GNAI1 | rs2465481 C/T Ancestral: C Minor: A | Cognition |
| rs2714465\_G | 45.0 | GNAI1 | rs2714465 A/G Ancestral: A Minor: G | Cognition |
| rs3092960\_A | 10.7 | CCR2 | rs3092960 A/G Ancestral: G Minor: A | Cognition |
| rs3131609\_C | 32.8 | USP50 | rs3131609 A/G Ancestral: A Minor: C | Cognition |
| rs360722\_A | 16.9 | IL18 | rs360722 C/T Ancestral: T Minor: A | Frail |
| rs3865444\_A | 27.1 | CD33 | rs3865444 G/T Ancestral: G Minor: A | Cognition |
| rs4147929\_A | 19.3 | ABCA7 | rs4147929 A/G Ancestral: G Minor: A | Cognition |
| rs429358\_C | 6.9 | APOE | rs429358 C/T Ancestral: C Minor: C | Cognition |
| rs4316\_T | 38.1 | ACE | rs4316 C/T Ancestral: C Minor: T | Cognition |
| rs4845622\_C | 38.6 | IL6R | rs4845622 A/C Ancestral: A Minor: C | Cognition |
| rs4968782\_G | 41.0 | **ACE** | rs4968782 A/G Ancestral: G Minor: G | Cognition |
| rs55636820\_A | 6.0 | BIN1 | rs55636820 A/G Ancestral: G Minor: A | Cognition |
| rs562020\_A | 34.6 | KLOTHO | rs562020 C/T Ancestral: T Minor: A | Cognition |
| rs573521\_A | 47.2 | MMP3 | rs573521 C/T Ancestral: C Minor: A | Cognition |
| rs5744256\_G | 18.3 | IL18 | rs5744256 C/T Ancestral: T Minor: G | Frail |
| rs603050\_T | 31.3 | WTAPP1 | rs603050 A/G Ancestral: G Minor: T | Cognition |
| rs611646\_T | 48.6 | ATM | rs611646 A/T Ancestral: A Minor: A | Frail |
| rs61812598\_A | 37.9 | IL6-R | rs61812598 A/G Ancestral: G Minor: A | Cognition |
| rs6441977\_A | 10.2 | CCRL2 | rs6441977 A/G Ancestral: G Minor: A | Cognition |
| rs650108\_A | 30.1 | MMP3 | rs650108 A/G Ancestral: G Minor: A | Cognition |
| rs6762266\_C | 10.4 | **CCRL2** | rs6762266 C/T Ancestral: T Minor: C | Cognition |
| rs679620\_T | 46.7 | MMP3 | rs679620 A/G Ancestral: G Minor: T | Cognition |
| rs6808835\_T | 10.5 | CCRL2 | rs6808835 G/T Ancestral: T Minor: T | Cognition |
| rs7110631\_C | 31.2 | **PICALM** | rs7110631 C/G Ancestral: G Minor: C | Cognition |
| rs7396366\_C | 36.0 | AP2A2 | rs7396366 G/T Ancestral: T Minor: C | Cognition |
| rs7412\_T | 6.6 | APOE | rs7412 C/T Ancestral: C Minor: T | Cognition |
| rs7497104\_T | 28.6 | MYO9A | rs7497104 C/T Ancestral: T Minor: T | Cognition |
| rs7926920\_A | 46.9 | WTAPP1 | rs7926920 A/G Ancestral: G Minor: A | Cognition |
| rs9267487\_C | 6.5 | DDX39B | rs9267487 C/T Ancestral: T Minor: C | Frail |
| rs9349407\_C | 24.5 | CD2AP | rs9349407 C/G Ancestral: G Minor: C | Cognition |
| rs948399\_C | 26.9 | MMP3 | rs948399 C/T Ancestral: T Minor: C | Cognition |
| rs9527025\_C | 14.8 | KLOTHO | rs9527025 C/G Ancestral: C Minor: C | Cognition |
| rs3219484\_T | 3.8 | MUTYH | rs3219484\_ A/G Ancestral: G Minor: T | Cognition |
| rs12752888\_C | 26.8 | **ACOT11**/LOC105378734 | rs12752888 C/T Ancestral: T Minor: C | Cognition |
| rs1539053\_A | 45.6 | DAB1 | rs1539053 C/T Ancestral: T Minor: G | Cognition |
| rs3811448\_A | 19.3 | TDRD10 | rs3811448 A/G Ancestral: A Minor: A | Cognition |
| rs4129267\_T | 37.9 | IL6-R | rs4129267 C/T Ancestral: C Minor: T | Cognition |
| rs915179\_G | 36.0 | LMNA | rs915179 A/G Ancestral: G Minor: A | Cognition |
| rs9919256\_A | 13.7 | LMNA | rs9919256 A/G Ancestral: A Minor: A | Cognition |
| rs6131\_T | 19.4 | SELP | rs6131 A/G Ancestral: A Minor: T | Frail |
| rs3818361\_A | 19.5 | CR1 | rs3818361 C/T Ancestral: C Minor: A | Cognition |
| rs1260326\_C | 46.3 | GCKR | rs1260326 C/T Ancestral: C Minor: T | Frail |
| rs744373\_G | 28.2 | **BIN1** | rs744373 C/T Ancestral: T Minor: G | Cognition |
| rs7561528\_A | 31.2 | **BIN1**/LOC105373605 | rs7561528 A/G Ancestral: A Minor: A | Cognition |
| rs11894266\_C | 43.5 | **SSB** | rs11894266 C/T Ancestral: C Minor: T | Cognition |
| rs6747918\_A | 49.2 | CASP8 | rs6747918 A/G Ancestral: A Minor: A | Frail |
| rs2929408\_A | 22.4 | KAT2B | rs2929408 G/T Ancestral: G Minor: A | Frail |
| rs737267\_T | 25.6 | SLC2A9 | rs737267 A/G/T Ancestral: G Minor: T | Frail |
| rs9461448\_G | 4.7 | PGBD1 | rs9461448 G/T Ancestral: T Minor: G | Cognition |
| rs9446432\_C | 8.2 | **C6orf155** | rs9446432 C/T Ancestral: T Minor: C | Cognition |
| rs9384428\_C | 32.5 | **MIR1202**/LOC101928923 | rs9384428 C/T Ancestral: T Minor: C | Cognition |
| rs4646450\_A | 16.4 | CYP3A5 | rs4646450 C/T Ancestral: T Minor: A | Frail |
| rs11767557\_C | 16.8 | EPHA1-AS1 | rs11767557 C/T Ancestral: T Minor: C | Cognition |
| rs11771145\_A | 32.9 | EPHA1-AS1 | rs11771145 A/G Ancestral: A Minor: A | Cognition |
| rs11136000\_T | 39.0 | CLU | rs11136000 C/T Ancestral: T Minor: T | Cognition |
| rs1157242\_T | 16.2 | **KCNU1** | rs1157242 A/G Ancestral: G Minor: T | Cognition |
| rs7840202\_C | 29.9 | UBR5 | rs7840202 A/C Ancestral: C Minor: C | Cognition |
| rs7920721\_G | 39.4 | ECHDC3 | rs7920721 A/G Ancestral: A Minor: G | Cognition |
| rs7905675\_A | 34.9 | **TFAM** | rs7905675 A/G Ancestral: A Minor: G | Cognition |
| rs17117126\_G | 9.5 | **CH25H** | rs17117126 A/G Ancestral: G Minor: G | Cognition |
| rs6265\_T | 21.6 | BDNF | rs6265 A/G Ancestral: G Minor: T | Cognition |
| rs1566729\_T | 14.1 | PTPRJ | rs1566729 A/G Ancestral: G Minor: T | Frail |
| rs583791\_C | 49.5 | MS4A6A | rs583791 A/G Ancestral: G Minor: C | Cognition |
| rs610932\_T | 48.5 | MS4A6A | rs610932 A/C Ancestral: A Minor: T | Cognition |
| rs662196\_C | 49.6 | MS4A6A | rs662196 A/G Ancestral: G Minor: C | Cognition |
| rs670139\_T | 31.2 | MS4A4E | rs670139 A/C/T Ancestral: C Minor: T | Cognition |
| rs676309\_C | 31.1 | MS4A4E | rs676309 A/G Ancestral: A Minor: C | Cognition |
| rs11827375\_A | 10.5 | **C11orf30** | rs11827375 A/G Ancestral: G Minor: A | Cognition |
| rs3851179\_T | 36.0 | **PICALM** | rs3851179 A/G Ancestral: G Minor: T | Cognition |
| rs541458\_C | 31.6 | **PICALM** | rs541458 C/T Ancestral: T Minor: C | Cognition |
| rs10501927\_G | 23.6 | CNTN5 | rs10501927 G/T Ancestral: T Minor: G | Cognition |
| rs495366\_A | 30.1 | WTAPP1 | rs495366 A/G Ancestral: G Minor: A | Cognition |
| rs645419\_A | 46.7 | MMP3 | rs645419 A/G Ancestral: G Minor: A | Cognition |
| rs10502262\_T | 27.7 | SORL1 | rs10502262 A/G Ancestral: G Minor: T | Cognition |
| rs1614735\_G | 47.6 | SORL1 | rs1614735 G/T Ancestral: T Minor: G | Cognition |
| rs2298813\_A | 4.0 | SORL1 | rs2298813 A/G Ancestral: G Minor: A | Cognition |
| rs3781835\_A | 2.3 | SORL1 | rs3781835 A/G Ancestral: G Minor: A | Cognition |
| rs4935774\_C | 20.5 | SORL1 | rs4935774 C/T Ancestral: C Minor: C | Cognition |
| rs4363657\_C | 15.2 | SLCO1B1 | rs4363657 C/T Ancestral: T Minor: C | Frail |
| rs1799986\_T | 17.4 | LRP1 | rs1799986 A/C/T Ancestral: C Minor: T | Frail |
| rs398655\_C | 45.0 | KLOTHO | rs398655 G/T Ancestral: G Minor: A | Cognition |
| rs648202\_T | 13.7 | KLOTHO | rs648202 C/T Ancestral: C Minor: T | Cognition |
| rs9526984\_G | 7.4 | KLOTHO | rs9526984 A/G Ancestral: A Minor: G | Cognition |
| rs9527024\_A | 14.8 | KLOTHO | rs9527024 A/G Ancestral: A Minor: A | Cognition |
| rs9536314\_G | 14.7 | KLOTHO | rs9536314 A/G/T Ancestral: T Minor: G | Cognition |
| rs2287396\_T | 17.7 | GSTZ1 | rs2287396 C/T Ancestral: C Minor: T | Frail |
| rs7175373\_C | 29.1 | **MYO9A** | rs7175373 A/C/G Ancestral: C Minor: C | Cognition |
| rs129968\_A | 39.8 | CREBBP | rs129968 A/G Ancestral: A Minor: G | Frail |
| rs3785880\_G | 39.8 | MAPT | rs3785880 G/T Ancestral: T Minor: G | Cognition |
| rs2526378\_G | 46.8 | TSPOAP1 | rs2526378 C/T Ancestral: C Minor: A | Cognition |
| rs4343\_A | 40.1 | ACE | rs4343 A/G Ancestral: A Minor: G | Cognition |
| rs4459609\_C | 40.9 | **ACE** | rs4459609 A/C Ancestral: A Minor: C | Cognition |
| rs3764650\_G | 11.8 | ABCA7 | rs3764650 G/T Ancestral: T Minor: G | Cognition |
| rs157580\_G | 39.1 | TOMM40 | rs157580 A/G Ancestral: G Minor: G | Cognition |
| rs2075650\_G | 7.5 | TOMM40 | rs2075650 A/G Ancestral: G Minor: G | Cognition |
| rs405509\_T | 42.8 | APOE | rs405509 A/C Ancestral: C Minor: T | Cognition |
| rs597668\_C | 12.0 | **EXOC3L2** | rs597668 C/T Ancestral: C Minor: C | Cognition |
| rs6859\_A | 38.8 | NECTIN2 | rs6859 A/G Ancestral: G Minor: A | Cognition |
| rs8106922\_G | 44.8 | TOMM40 | rs8106922 A/G Ancestral: A Minor: G | Cognition |
| rs17411904\_C | 7.7 | **PCK1** | rs17411904 C/T Ancestral: T Minor: C | Cognition |
| rs2833383\_T | 27.9 | TIAM1 | rs2833383 C/T Ancestral: C Minor: T | Frail |
| rs4646316\_T | 27.7 | COMT | rs4646316 C/T Ancestral: C Minor: T | Frail |
| rs4680\_A | 46.4 | COMT | rs4680 C/T Ancestral: G Minor: A | Cognition |
| rs740234\_G | 24.2 | TCN2 | rs740234 C/T Ancestral: T Minor: G | Frail |

*Notes:* \*Proxy SNP, Cog/Frail – variant was found for both phenotypes in the systematic review, bold text indicates the closest gene

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