SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TEXT

Cohort description

The Age, Gene/Environment Susceptibility-Reykjavik (AGES)

The Reykjavik Study cohort originally comprised a random sample of 30,795 men and women born in 1907–1935 and living in Reykjavik in 1967 [1]. A total of 19381 attended, resulting in 71% recruitment rate. The study sample was divided into six groups by birth year and birth date within month. One group was designated for longitudinal follow-up and was examined in all stages. One group was designated a control group and was not included in examinations until 1991. Other groups were invited to participate in specific stages of the study. Between 2002 and 2006, the AGES-Reykjavik study re-examined 5764 survivors of the original cohort who had participated before in the Reykjavik Study. Of those, 3,219 have genomic genotypes and only 3,166 went through gait assessment that included 6 meter walk in usual pace.

The Atherosclerosis Risk in Communities (ARIC)

The ARIC study is a population-based cohort study of atherosclerosis and clinical atherosclerotic diseases [2]. At its inception (1987-1989), 15,792 men and women, including 11,478 white and 4,266 black participants were recruited from four U.S. communities: Suburban Minneapolis, Minnesota; Washington County, Maryland; Forsyth County, North Carolina; and Jackson, Mississippi. In the first 3 communities, the sample reflects the demographic composition of the community. In Jackson, only black residents were enrolled. Participants were between age 45 and 64 years at their baseline examination in 1987-1989 when blood was drawn for DNA extraction and participants consented to genetic testing. Between 2004 and 2006, participants who had undergone magnetic resonance scanning at the third ARIC visit were invited to participate in the ARIC MRI study [3]. Gait assessment was performed on 1134 ARIC participants. Time to walk 25 feet (7.62 m) at the participants' usual pace was recorded in an unobstructed corridor with a stop watch. Four hundred and forty five participants of European ancestry with genome-wide genotype data and a gait speed measurement were enrolled to this study.

Baltimore Longitudinal study on Aging (BLSA)

The Baltimore longitudinal study on Aging (BLSA) study is a population-based study aimed to evaluate contributors of healthy aging in the older population residing predominantly in the Baltimore-Washington DC area [4]. Starting in 1958, participants are examined every one to four years depending on their age. Currently there are approximately 1100 active participants enrolled in the study. Blood samples were collected for DNA extraction, and genome-wide genotyping was completed for 1231 subjects using Illumina 550K. This analysis focused on a subset of the participants (N=334) with European ancestry with data on walking speed (6 meter walk in normal pace). The BLSA has continuing approval from the Institutional Review Board (IRB) of Medstar Research Institute.

Cardiovascular Health Study (CHS)

The CHS is a population-based cohort study of risk factors for CHD and stroke in adults ≥65 years conducted across four field centers [5].The original predominantly Caucasian cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists; subsequently, an additional predominantly African-American cohort of 687 persons were enrolled for a total sample of 5,888. Only 3980 CHS participants who were free of CVD at baseline, consented to genetic testing, and had DNA available for genotyping were GWASed. Finally, to maintain race homogeneity we picked 3184 Caucasian with gait speed (4.6 meter walk normal pace) and genome wide assessments to participate in the current study.

Framingham Heart Study (FHS)

The FHS is a longitudinal community-based multi-generational study funded by the National Heart Lung and Blood Institute [6]. The Original cohort (Gen1) has undergone 32 biennial examinations since 1948; the Offspring cohort (Gen2) has participated in 9 exams from 1971 onwards, and the Omni group 1 cohort in 4 examinations from 1994 onwards. The Gen3 and Omni group 2 cohorts completed 2 examinations since 2002 and are currently starting the third examination cycle (April 2016). All participants undergo extensive research examinations and surviving Original cohort, Offspring and Gen 3 participants had genome-wide genotyping with the Affymetrix 500K Array Set and 50K Human Gene Focused Panel available at the start of this study [7]. At Offspring exam 8 (2005-2008) and Original cohort exam 26 (1999-2001), participants were asked to walk a 4 meter course at a normal pace while being timed with a stop watch by trained technicians. The usual pace walk was repeated and the faster of the two walks was used for analysis. Participants were excluded if under age 60. The final sample included 2384 participants (56.1% women), mean age 72.4 (SD 8.5) years (range 60 to 98) with gait speed and genomic

genotyping assessed. Informed consent was obtained at each attended exam and the Boston University Medical Center Institutional Review Board approved the protocol for all examinations.

Health, Aging, and Body Composition Study (HABC)

The Health Aging and Body Composition (HABC) Study is a NIA-sponsored cohort study of the factors that contribute to incident disability and the decline in function of healthier older persons, with a particular emphasis on changes in body composition in old age. Between March 1997 and July 1998, 3075 70-79 year old community-dwelling adults (41% African-American) were recruited to participate in the Health ABC Study; characteristics of the cohort have been described elsewhere [8]. Medicare beneficiary listings were used to recruit in metropolitan areas surrounding Pittsburgh, Pennsylvania, and Memphis, Tennessee. Eligibility criteria included having no difficulty walking one-quarter of a mile, climbing 10 steps, or performing activities of daily living (transferring, bathing, dressing, and eating); no history of active treatment for cancer in the prior 3 years; and no plans to move from the area within 3 years. Genotyping was successful for 2,802 unrelated individuals (1663 Caucasians and 1139 African Americans). To reduce race bias we include only Caucasians of which 1482 have their gait speed assessed in normal pace (6 meter walk) have enrolled to the study.

Health and Retirement Study (HRS)

The Health and Retirement Study (HRS) is a longitudinal survey of a representative sample of Americans over the age of 50 [9]. The current sample is over 26,000 persons in 17,000 households. Respondents are interviewed every two years about income and wealth, health and use of health services, work and retirement, and family connections. DNA was extracted from saliva collected during a face-to-face interview in the respondents' homes. These data represent respondents who provided DNA samples and signed consent forms in 2006 and 2008. Gait speed was measured only on respondents ≥ 65 years of age. Respondents were removed if they had gait velocities <0.05 or gait velocities > 5sd from the mean. A total of 5,073 subjects who have both a measure of gait speed (2.5 meter walk at a normal pace) and high quality imputed genomic genotypes were included in the analysis.

Invecchiare in Chianti (InCHIANTI)

The InCHIANTI study is a population-based epidemiological study aimed at evaluating the factors that influence mobility in the older population living in the Chianti region in Tuscany, Italy [10]. The details of the study have been previously reported. Briefly, 1616 residents were selected from the population registry of Greve in Chianti (a rural area: 11,709 residents with 19.3% of the population greater than 65 years of age), and Bagno a Ripoli (Antella village near Florence; 4,704 inhabitants, with 20.3% greater than 65 years of age). The participation rate was 90% (n=1453), and the subjects ranged between 21-102 years of age. Overnight fasted blood samples were for genomic DNA extraction. Illumina Infinium HumanHap 550K SNP arrays were used for genotyping. Data from 898 subjects were used for this analysis with genetic and walking speed (4 meter walk in normal pace) data. The study protocol was approved by the Italian National Institute of Research and Care of Aging Institutional Review and Medstar Research Institute (Baltimore, MD).

Lothian Birth Cohorts 1921 (LBC1921) and 1936 (LBC1936)

The Lothian Birth Cohorts include surviving participants from the Scottish Mental Surveys of 1932 or 1947 (SMS1932 and SMS1947), having been born, respectively in 1921 (LBC1921) and 1936 (LBC1936) [11-13]. The LBC1921 cohort consists of 550 relatively healthy individuals, 316 females and 234 males, assessed on cognitive and medical traits at about 79 years of age. When tested, the sample had a mean age of 79.1 years (SD = 0.6). The LBC1936 consists of 1091 relatively healthy individuals assessed on cognitive and medical traits at about 70 years of age. At baseline the sample of 548 men and 543 women had a mean age 69.6 years (SD = 0.8). They were all Caucasian and almost all lived independently in the Lothian region (Edinburgh city and surrounding area) of Scotland. Genotyping was performed at the Wellcome Trust Clinical Research Facility, Edinburgh. Among participants with genome-wide data and gait speed assessment (6 meter walk in normal pace), 510 (LBC1921) and 1001 (LBC1936) individuals were available for the present analysis.

Osteoporotic Fractures in Men Study (MrOS)

The Osteoporotic Fractures in Men Study (MrOS) is a multi-center prospective, longitudinal, observational study of risk factors for vertebral and all non-vertebral fractures in older men, and of the sequelae of fractures in men [14, 15]. MrOS study population consists of 5,994 community dwelling, ambulatory men aged 65 years or older from six communities in the United States (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Monongahela Valley near Pittsburgh, PA; Portland, OR; and San Diego, CA). Inclusion criteria were designed to provide a study cohort that is representative

of the broad population of older men. Genomic DNA from participants in the Osteoporotic Fractures in Men (MrOS) Study was extracted from whole blood samples collected at the baseline visit using the Flexigene protocol (Qiagen, Valencia, CA, USA) at the University of Pittsburgh. Among the 5994 MrOS participants enrolled at the baseline visit, 5130 samples with whole genome genotyping data that passed QC. Of which, only 4,643 with gait speed assessed in normal pace (6 meter walk) were enrolled to the study.

The Religious Orders Study and Rush Memory and Aging Project (ROSMAP)

Data came from 2 community based cohort studies of aging and dementia, the Religious Orders Study and Rush Memory and Aging Project (ROSMAP). Details about the study design have been described previously [16, 17]. Both studies were approved by the institutional review board of Rush University Medical Center. Participants were free of known dementia at enrollment and agreed to annual clinical evaluation and brain donation at the time of death. An informed consent and an Anatomic Gift Act form were obtained from each participant. The follow-up rate among the survivors exceeds 90%. The two studies are conducted by the same team of investigators and share a large common core of test batteries, which allows combined analysis of the data. Gait speed was derived by timing with a stop watch how long it took a participant to walk 8 feet (2.5m) at their usual pace [18]. DNA was extracted from whole blood, lymphocytes, or frozen postmortem brain tissue. Genotyping was performed at the Broad Institute's Center for Genotyping and the Translational Genomics Research Institute [19]. Among participants with genome-wide data and gait speed assessment 1,646 individuals were available for the present study.

Rotterdam Study (RSI, -II, -III)

The Rotterdam Study is a population-based study in Rotterdam that currently investigates 14,926 inhabitants from a suburb of the city aged 45 years or over. Participants were enrolled during three recruitment phases – in 1990 (cohort 1), 2000 (cohort 2), and 2006 (cohort 3) [20, 21]. Visits to the research center are planned every 3-4 years for various medical examinations. Genotyping was successfully performed on 11,496 participants. Gait assessment was introduced in the study protocol in 2009. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands , implementing the Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study). All participants provided written informed consent to participate in the study and to obtain information from their treating physicians. Gait assessment of 3651 subjects included 5.79-m long pressure-activated walkway (GAITRite Platinum; CIR systems, Sparta, NJ: 4.88-m active area; 120-Hz sampling rate) [22, 23]. Follow thorough exclusion the reminder 2911 subjects were genomic genotyped and imputed to the HapMap 2 reference panel.

Study of Osteoporotic Fractures (SOF)

The Study of Osteoporotic Fractures (SOF) is a prospective multicenter study of risk factors for vertebral and non-vertebral fractures [24]. The cohort is comprised of 9704 community dwelling women 65 years old or older recruited from populations-based listings in four U.S. areas: Baltimore, Maryland; Minneapolis, Minnesota; Portland, Oregon; and the Monongahela Valley, Pennsylvania. Women enrolled in the study were 99% Caucasian with African American women initially excluded from the study due to their low incidence of hip fractures. The SOF participants were followed up every four months by postcard or telephone to ascertain the occurrence of falls, fractures and changes in address. To date, follow-up rates have exceeded 95% for vital status and fractures, a review of pre-operative radiographs. The SOF study recruited only women. Among the 9704 SOF participants enrolled at the baseline visit, 3625 samples with whole genome genotyping data that passed QC. Of which, only 3,441 with gait speed assessed in normal pace (6 meter walk) were enrolled to the study.

Tasmanian Study of Cognition and Gait (TASCOG)

TASCOG is a study of cerebrovascular mechanisms underlying gait, balance and cognition in a population-based sample of Tasmanian people aged at least 60 years [25]. Individuals aged 60–86 years (n = 395) living in Southern Tasmania, Australia, were randomly selected from the electoral roll between 2006 and 2008 to participate in the study. Individuals were excluded if they lived in a nursing home, had a contraindication for magnetic resonance scanning (MRI) or were unable to walk without a gait aid. The response rate was 55%, and genotyping was performed at the Diamantina Institute, University of Queensland. The study was approved by the Human Health and Medical Research Ethics Committee, University of Tasmania. Genomic data and gait speed assessment (GAITRite) were available for 360 subjects that are part of this study.

Genetic Epidemiology Network of Arteriopathy (GENOA)

The Genetic Epidemiology Network of Arteriopathy (GENOA) study consists of hypertensive sibships

recruited for linkage and association studies in order to identify genes that influence blood pressure and its target organ damage [26]. In the initial phase of the GENOA study (Phase I: 1996-2001), all members of sibships containing ≥ 2 individuals with essential hypertension clinically diagnosed before age 60 were invited to participate, including both hypertensive and normotensive siblings. In the second phase of the GENOA study (Phase II: 2000-2004), 1239 European American participants were successfully re-recruited to measure potential target organ damage due to hypertension. From 2001-2006, Phase II GENOA participants that had a sibling willing and eligible to participate underwent a neurocognitive testing battery to assess several domains of cognitive and neurological functioning, including the assessment of gait speed (N=967). Participants were excluded from this analysis if they were less than 60 years of age or gait velocities >1.9m/s. The sample includes 471 European Americans (55.0% female) with imputed genotypes and a measure of gait speed on a 25 foot (7.6 meter) walking course.

Leiden Longevity Study (LLS)

The LLS has been designed to investigate biomarkers of healthy ageing and longevity [27] and has been described in detail previously [28]. It is a family-based study consisting of 1,671 offspring of 421 nonagenarian sibling pairs of Dutch descent, and their 744 partners. DNA from the LLS was extracted from white blood cells at baseline using conventional methods and genotyping was performed with Illumina Human660W-Quad and OmniExpress BeadChips (Illumina, San Diego, CA, USA). Imputation was performed with IMPUTE using the HapMap 2 reference panel [29]. Walking speed at usual pace was determined over 4 meters. Among participants with genome-wide data and gait speed assessment 235 individuals were available for the present study.

Osteoporotic Fractures in Men Study (MrOS) Sweden (Malmö[MrOSMalmo] and Gothenburg [MrOSGBG])

The Osteoporotic Fractures in Men (MrOS) study is a multicenter, prospective study including older men in Sweden, Hong Kong and the United States. The MrOS Sweden study (n=3014) [30] consists of three sub-cohorts from three different Swedish cities (n=1005 in Malmö, n=1010 in Gothenburg, and n=999 in Uppsala). Study subjects (men aged 69 to 81 years) were randomly identified using national population registers. A total of 62% of the MrOS Sweden subjects who have both GAIT information and high quality imputed genomic genotypes participated in the study (n=922 in Malmö, n=960 in Gothenburg). To be eligible for the study, the subjects had to be able to walk without assistance, provide self-reported data, and sign an informed consent. The study was approved by the ethics committees at the Universities of Gothenburg, Lund, and Uppsala. Informed consent was obtained from all study participants. Genome-wide genotyping was performed in the MrOS Gothenburg and MrOS Malmö sub cohorts. Walking speed at usual pace was determined over 6 meters. Both duration of the walk and the number of steps were measured.

Expression quantitative trait loci (eQTL) analysis

A general overview of a subset of >50 eQTL studies has been published [31], with specific citations for >100 datasets included in the current query following here. Blood cell related eQTL studies included fresh lymphocytes [32], fresh leukocytes [33], leukocyte samples in individuals with Celiac disease [34], whole blood samples [35-54], lymphoblastoid cell lines (LCL) derived from asthmatic children [55, 56], HapMap LCL from 3 populations [57], a separate study on HapMap CEU LCL [58], additional LCL population samples [59-65], neutrophils [66, 67], CD19+ B cells [68], primary PHA-stimulated T cells [62, 65], CD4+ T cells (20833654), peripheral blood monocytes [59, 68-72], long non-coding RNAs in monocytes [73] and CD14+ monocytes before and after stimulation with LPS or interferon-gamma [74], CD11+ dendritic cells before and after Mycobacterium tuberculosis infection [75] and a separate study of dendritic cells before or after stimulation with LPS, influenza or interferon-beta [76]. Micro-RNA QTLs [77, 78], DNase-I QTLs [79], histone acetylation QTLs [80], and ribosomal occupancy QTLs [81] were also queried for LCL. Splicing QTLs [82] and micro-RNA QTLs [83] were queried in whole blood.

Non-blood cell tissue eQTLs searched included omental and subcutaneous adipose [37, 48, 54, 63, 84], visceral fat [37] stomach [84], endometrial carcinomas [85], ER+ and ER- breast cancer tumor cells [86], liver [37, 84, 87-90], osteoblasts [91], intestine [92] and normal and cancerous colon [93, 94], skeletal muscle [37, 95], breast tissue (normal and cancer] [96, 97], lung [48, 98-101], skin [48, 59, 63, 102], primary fibroblasts [62, 65, 103], sputum [104], pancreatic islet cells [105], prostate [106], rectal mucosa [107], arterial wall [37] and heart tissue from left ventricles [48, 108] and left and right atria [109]. Micro-RNA QTLs were also queried for gluteal and abdominal adipose [110] and liver [111]. Methylation QTLs were queried in pancreatic islet cells [112]. Further mRNA and micro-RNA QTLs were queried from ER+ invasive breast cancer samples, colon-, kidney renal clear-, lung- and prostate-adenocarcinoma samples [113].

Brain eQTL studies included brain cortex [36, 72, 114-116], cerebellar cortex [117], cerebellum [115, 118-121], frontal cortex [117, 119, 121], gliomas [122], hippocampus [117, 119], inferior olivary nucleus (from medulla) [117], intralobular white matter [117], occipital cortex [117], parietal lobe [120], pons [121], pre-frontal cortex [118, 119, 123, 124], putamen (at the level of anterior commissure) [117], substantia nigra [117], temporal cortex [115, 117, 119, 121], thalamus [119] and visual cortex [118].

Additional eQTL data was integrated from online sources including ScanDB, the Broad Institute GTEx Portal, and the Pritchard Lab (eqtl.uchicago.edu). Cerebellum, parietal lobe and liver eQTL data was downloaded from ScanDB and cis-eQTLs were limited to those with P<1.0E-6 and trans-eQTLs with P<5.0E-8. Results for GTEx Analysis V4 for 13 tissues were downloaded from the GTEx Portal and then additionally filtered as described below www.gtexportal.org: thyroid, leg skin (sun exposed), tibial nerve, aortic artery, tibial artery, skeletal muscle, esophagus mucosa, esophagus muscularis, lung, heart (left ventricle), stomach, whole blood, and subcutaneous adipose [48]. Splicing QTL (sQTL) results generated with sQTLseeker with false discovery rate P≤0.05 were retained. For all gene-level eQTLs, if at least 1 SNP passed the tissue-specific empirical threshold in GTEx, the best SNP for that eQTL was always retained. All gene-level eQTL SNPs with P<1.67E-11 were also retained, reflecting a global threshold correction of P=0.05/(30,000 genes X 1,000,000 tests).

Analysis Plan

1) Analysis Plan:

a. Imputation: all cohorts have imputed to HapMap, using either BimBam or MACH.

b. Cohort-specific analyses

i. Multiple linear regression of imputed SNPs on gait speed (m/s)

ii. All analyses will be sex-combined

iii. SNPs will be coded as additive model as a count of the number of variant alleles present (1 degree of freedom).

iv. Covariate adjustment:

1. age (at time of exam)
2. gender
3. study site (for cohorts with multiple sites)
4. principal components that control for population stratification (in some cohorts)
5. height
6. Osteoarthritis*

c. Meta-analysis: Inverse variance weighted meta-analysis to be performed on summary statistics of imputed data. Meta-analysis of gait speed outcome will be performed using a fixed effects model of beta estimates and standard errors from each cohort.

i. Significance threshold: A threshold of p-value 5x10-8 will be used to determine genome-wide statistical significance.

*Cohorts with Osteoarthritis measurement will add a variable yes/no converted to 1/0 for any sort of osteoarthritis and will provide two analyses one with and one without this variable.

– Cohorts without Osteoarthritis measurement will stick to the original analytic plan.

– Cohorts with Osteoarthritis measurement will provide:

I. Analysis which includes everyone with or without osteoarthritis.

II. Analysis only for the one without this variable.

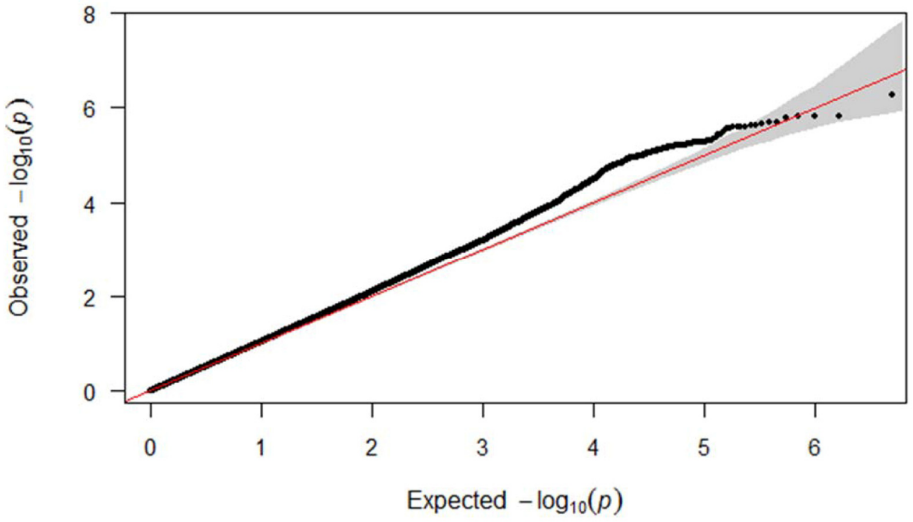
d. Cohorts with mixed ethnicity will be stratified by race. Meta analysis will test both possibilities with the additional race as a separate cohort and without.

2) Data format: The data delivery format for the meta-analysis will be according to the CHARGE protocol for file sharing.

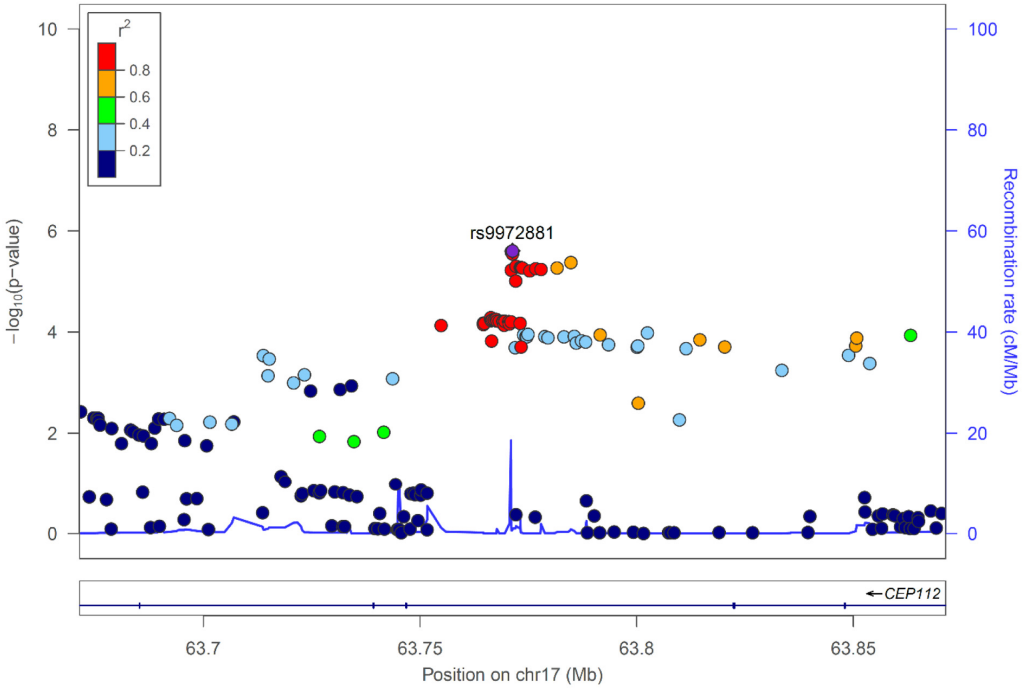
a. ShareSpaces, a secure web-based file-sharing system implemented by the University of Washington's Catalyst computing group, will be used.

b. The following variables should be included when sharing imputed results for meta-analysis (Table 11).

SUPPLEMENTARY FIGURES

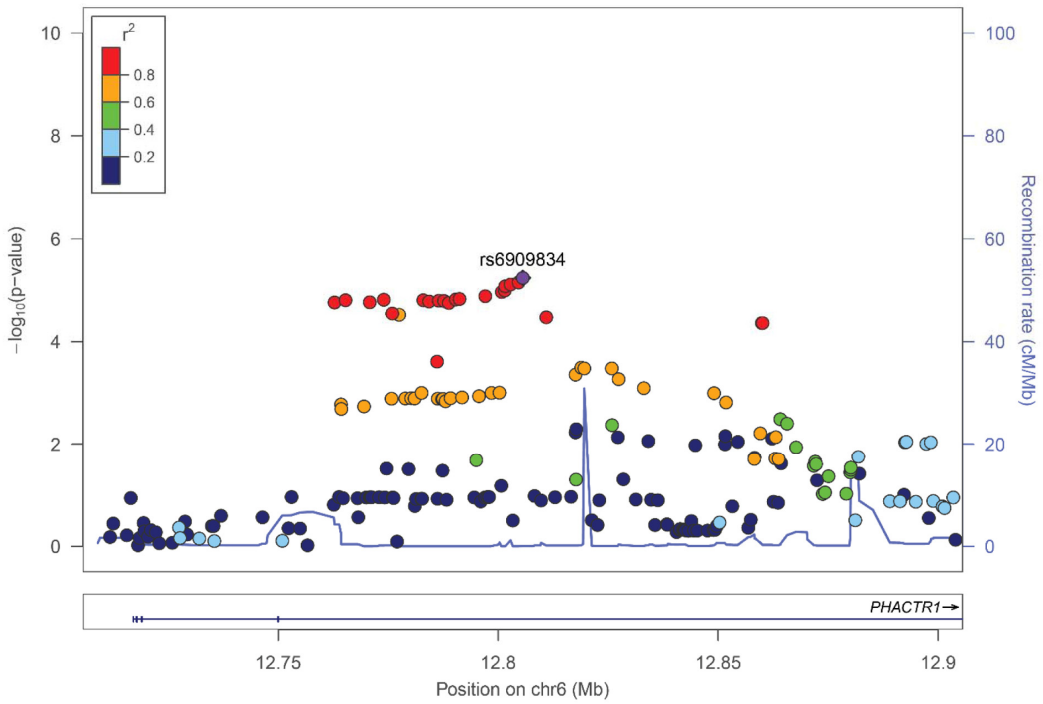


Supplementary Figure 1. Q-Q plot of expected (red line) vs. observed (black dot line) –log10 p-values for meta-analysis of genome-wide association studies of gait speed.



A

B


r²
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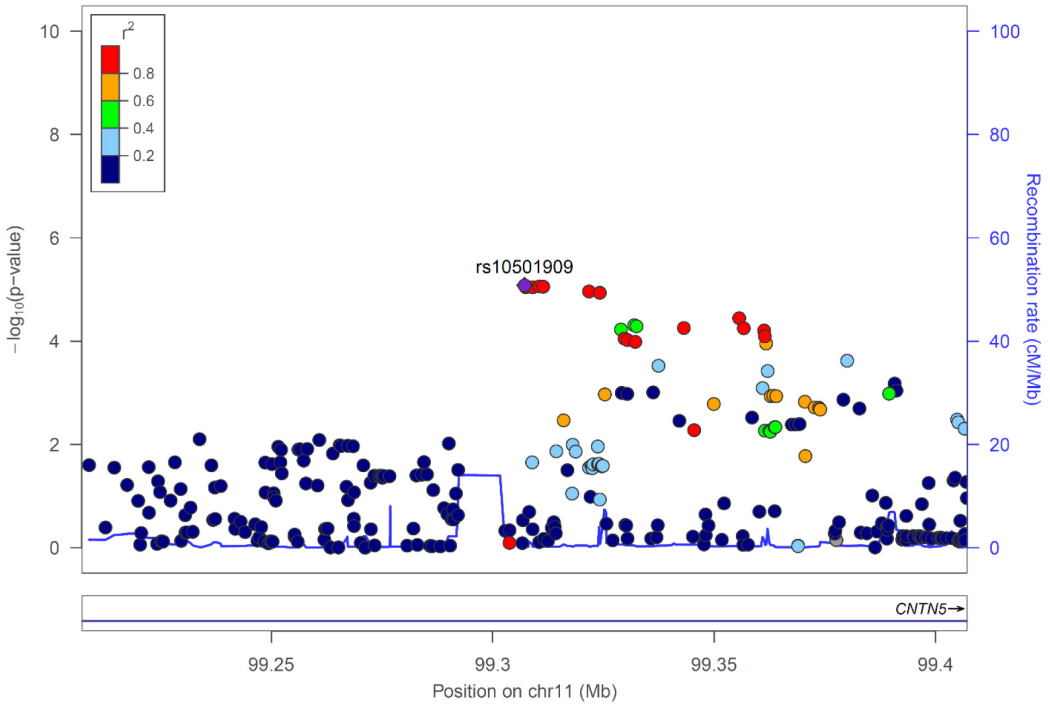
0.6
0.4
0.2
rs6909834
−log10(p−value)
Recombination rate (cM/Mb)
PHACTR1
12.75
12.8
12.85
12.9
Position on chr6 (Mb)

C


r²
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0.6
0.4
0.2
rs10501909
−log10(p−value)
Recombination rate (cM/Mb)
CNTN5
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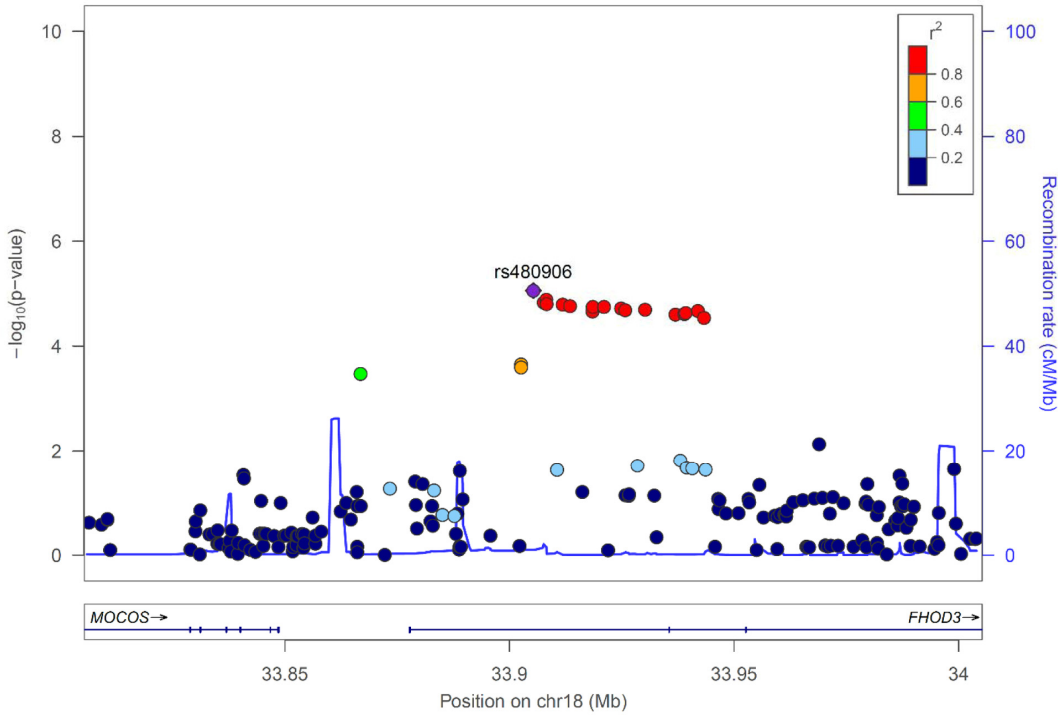
99.3
99.35
99.4
Position on chr11 (Mb)

D


r²
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0.6
0.4
0.2
rs480906
−log10(p−value)
Recombination rate (cM/Mb)
MOCOS→
FHOD3→
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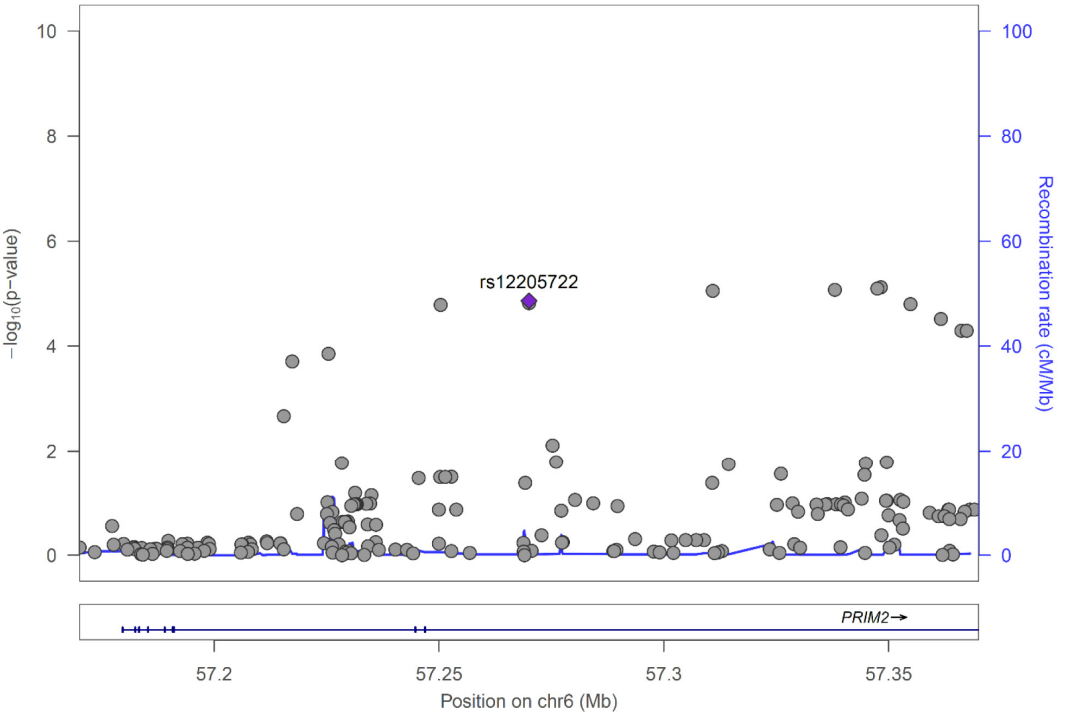
33.9
33.95
34
Position on chr18 (Mb)

E


rs12205722
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Recombination rate (cM/Mb)
PRIM2→
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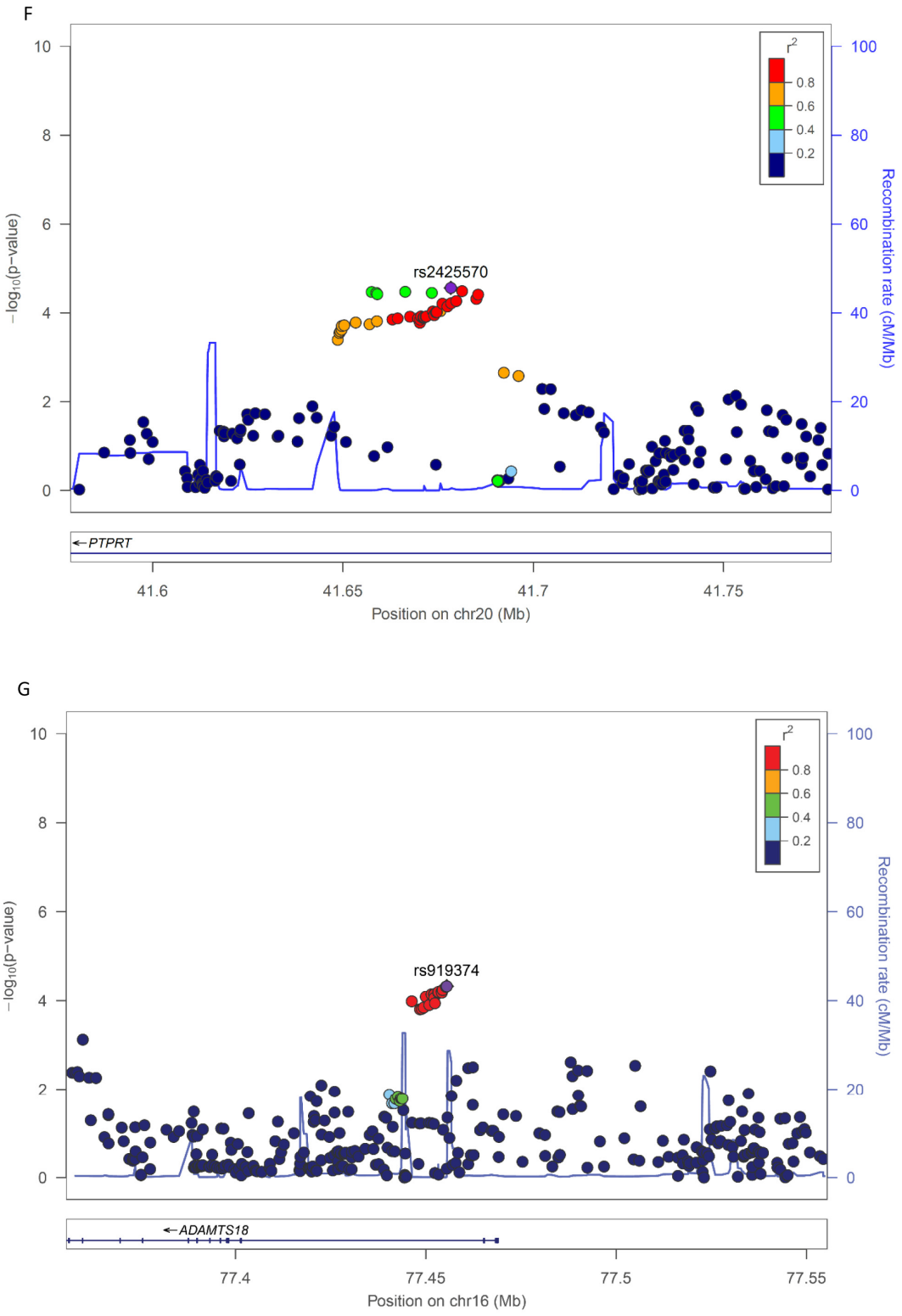
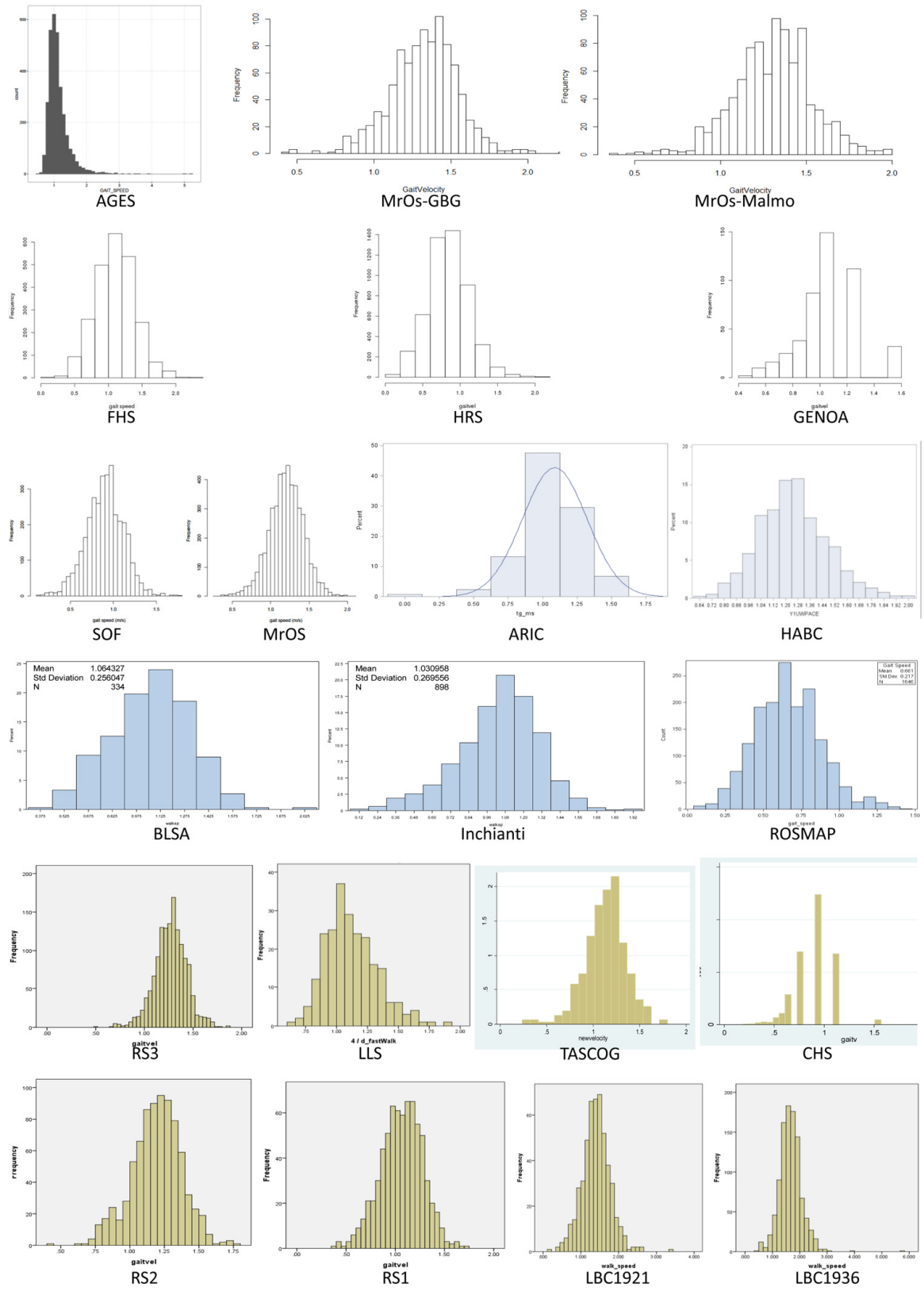
57.25
57.3
57.35
Position on chr6 (Mb)



Supplementary Figure 2. LocusZoom plots for the genes (7 genes) with most suggestive variants (not listed in the top tens) associated with gait speed of the combined analysis (**A**) *CEP112*; (**B**) *PHACTR1*, (**C**) *CNTN5*, (**D**) *FHOD3*, (**E**) *PRIM2*, (**F**) *PTPRT*, (**G**) *ADAMTS18*). In each plot, the −log10 of *p* values are on the left *y*-axis; the SNP genomic position (HG19) on the *x*-axis; the estimated recombination rate from 1000 genomes Nov. 2014 EUR are on the right *y*-axis and plotted in blue. The most significant SNP is in purple diamond and plotted using the *p* value attained from the meta-analysis. SNPs are colored to reflect linkage disequilibrium (LD) with the most significant SNP in red (pairwise *r*2 from 1000 genomes Nov. 2014 EUR). Gene annotations are from the SeattleSeqAnnotation141.



Supplementary Figure 3. Gait speed values distribution within cohorts.

SUPPLEMENTARY TABLES

Please browse links in Full Text version to see Supplementary Tables S1-S10.

SUPPLEMENTARY REFERENCES

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