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ORIGINAL ARTICLE

A genome-wide association study of frailty identifies significant genetic correlation with neuropsychiatric, cardiovascular, and inflammation pathways

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Abstract Frailty is an aging-related clinical phenotype defined as a state in which there is an increase in a person's vulnerability for dependency and/or mortality when exposed to a stressor. While underlying mechanisms leading to the occurrence of frailty are complex, the importance of genetic factors has not been fully investigated. We conducted a large-scale genome-wide association study (GWAS) of frailty, as defined by the five criteria (weight loss, exhaustion, physical activity, walking speed, and grip strength) captured in the Fried Frailty Score (FFS), in 386,565 European descent participants enrolled in the UK Biobank (mean age 57 [SD 8] years, 208,481 [54%] females). We identified 37 independent, novel loci associated with the FFS ($p < 5 \times 10^{-8}$), including seven loci without prior described associations with other traits. The variants associated with FFS were significantly enriched in brain tissues as well as aging-related pathways. Our post-GWAS bioinformatic analyses revealed significant genetic correlations between FFS and cardiovascular-, neurological-, and inflammation-related diseases/traits, and subsequent Mendelian Randomization analyses identified causal associations with chronic pain, obesity, diabetes, education-related traits, joint disorders,

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and depressive/neurological, metabolic, and respiratory diseases. The GWAS signals were replicated in the Health and Retirement Study (HRS, $n = 9{,}720$, mean age 73 [SD 7], 5,582 [57%] females), where the polygenic risk score built from UKB GWAS was significantly associated with the FFS in HRS individuals (OR per SD of the score 1.27, 95% CI 1.22–1.31, $p = 1.3 \times 10^{-11}$). These results provide new insight into the biology of frailty by comprehensively evaluating its genetic architecture.

Keywords Frailty · GWAS · Genetic correlation · Polygenic risk score · Aging

Introduction

As the proportion of older adults rise around the globe, frailty has increasingly become the focus of attention among researchers and clinicians. Frailty can be defined as a medical condition characterized by a progressive decline in physiological systems that increases an individual's vulnerability to adverse health outcomes when exposed to a stressor [1]. Most prevalent in the elderly, frailty is not an inevitable consequence of the aging process; rather, frailty can be viewed as an accelerated or pathological state of aging. Frailty is associated with higher risks of disability, dementia, hospitalization, mortality, and poor outcomes after surgery, a constellation of findings that reflect both the importance and phenotypic complexity of this phenotype [1]. Moreover, frailty is related to increased healthcare costs and poor prognosis in surgical patients as well as with chronic renal failure, liver disease or cardiological conditions [2]. Novel preventive and therapeutic strategies are urgently needed to reduce the socioeconomic burden associated with the development and progression of frailty.

The main systems identified to date in the pathophysiology of frailty include the endocrine axis [3], inflammation/immune system [4], stress response [5] and metabolic pathways [6]. Multiple age-related hormone changes have been associated with frailty [3]. It has also been suggested that the immune system is involved in the development of frailty. Particularly, serum levels of the proinflammatory cytokine interleukin IL-6 [7], procalcitonin [7] and C-reactive protein (CRP) [7, 8], as well as white blood cell and monocyte counts [8], are elevated in frail adults. Other stress response and metabolic systems include altered glucose metabolism [9], dysregulation of the autonomic nervous system [10] and age-related changes in the renin-angiotensin system [11]. Given the observational design of most of the studies outlined above, it is difficult to judge whether the associations with these pathophysiological mechanisms represent true causal links or just the co-occurrence of frailty with the numerous disease that are highly prevalent in older adults.

In addition to the aforementioned observations, genetic studies using a candidate-gene design identified several genes associated with frailty, mostly related to inflammation, protein regulation, and cognitive function (with the epsilon variants within *APOE* playing a prominent role*)* [12, 13]. Importantly, previous genetic studies of frailty identified loci associated with traits such as body mass index (BMI), cardiovascular disease, smoking, HLA proteins, neuropathy, endocrine system, depression and neuroticism [13, 14]. However, these studies were limited by small sample size and their restriction to incident frailty, leading to diminished statistical power.

Further exploration of the genetic architecture of frailty will provide novel insights on the biological pathways involved in the development and progression of frailty and identify new targets for prevention and treatment. Here, we conducted a large-scale genome-wide association study (GWAS) of frailty in the UK Biobank (UKB) [15] comprising over 380,000 individuals of European ancestry and replicated the associations in 9,720 individuals from the Health and Retirement Study (HRS) [16]. In contrast to a recent genome-wide studies of frailty [17], we used the Fried Frailty Score (FFS) [18] instead of the Frailty Index (FI) to model frailty. While the FI requires a thorough clinical assessment, including laboratory work-up, the FFS uses a small number of signs and symptoms (weight loss, low physical activity, exhaustion, slowness, and weakness), thus facilitating applicability and reproducibility [19]. In addition, compared to this recent frailty GWAS, we maximized the discovery power by avoiding an age restriction and including more samples. The applicability of our findings to older adults was validated in a landmark study of aging—HRS.

Subjects and methods

Study design

We conducted a two-stage (discovery and replication) GWAS using publicly available data from two

established observational studies: the UKB and HRS. Research activities were approved by the corresponding local IRBs and written informed consent was obtained from all study participants or their legally appointed representatives. With the GWAS, we then performed a series of post-GWAS analyses to gain deeper understanding of the genetic basis of frailty, as illustrated in the flowchart in the Supplemental Data (Supp. Figure 1).

The UK biobank

The UKB is a large prospective study established to be a public resource for research into the causes of diseases in the UK population. The study protocol, details of the study design and information on data access are available online [15]. In brief, a total of 502,618 community-dwelling persons aged 40–69 years were recruited from across the United Kingdom between 2006 and 2010. We restricted the analysis to unrelated individuals of genetically-confirmed European ancestry [20].

Fried frailty score

The FFS developed by Fried et al. [18] is a well-established and validated standardized definition of frailty phenotype. It has been widely used in several large-scale studies, including both the UKB and HRS [21, 22]. Other frailty definitions exist, however, these are either lacking in validity evaluations or are too complex in their criteria [23]. The FFS offers a concise and generalizable method for defining frailty which enhances the applicability and reproducibility of GWAS results. Thus, in this study, we adopted the FFS definition to classify frailty status in our participants. Specifically, based on self-reported answers and physical measurements collected at enrollment, participants were assigned an FFS score of 0–5 according to the number of criteria met (weight loss, exhaustion, physical activity, walking speed, and grip strength) [18]. Although frailty is usually modeled as a binary variable, with FFS > = 3 classified as frailty. Here we analyzed this phenotype as an ordinal variable in order to reduce information loss and enhance the statistical power of the analysis. There were 35,588 (7.1%) participants excluded from analysis for missing one or more of the five frailty criteria at baseline.

GWAS analysis

We used phase three genotype data released by UKB [20] where the participants underwent genotyping with one of two closely related Affymetrix microarrays (UK BiLEVE Axiom Array or UK Biobank Axiom Array) for ~ 820,000 variants. Additional genotypes were imputed centrally using the 1000 Genomes [24] and Haplotype Reference Consortium (HRC) [25] reference panels, yielding ~ 93 million variants for each individual. We restricted the analysis to 8,883,488 autosomal variants with imputation quality score > 0.9, Hardy–Weinberg p-value > 1×10^{-6}, and minor allele frequency (MAF) > 0.01 and genotyping missing rate < 0.1. European samples were identified by a combination of self-reported and genetically confirmed ancestry based on principal component (PC) analysis of individuals' genotypes. Further sample exclusion criteria included poor heterozygosity or missingness, sex chromosome aneuploidy, and withdrawal of informed consent. We used BOLT-LMM (v2.3.2) to perform single-variant genome-wide association testing [26], including age, sex and the first 20 genetic principal components as covariates. We used Linkage Disequilibrium Score Regression (LDSC, v1.0.0) [27] to perform SNP-based heritability estimation. The level of bias in GWAS was estimated using both LDSC intercept and lambda GC.

Genomic risk loci definition

To identify independent associations, we conducted a conditional and joint (COJO) analysis of the GWAS results as implemented by GCTA, accounting for the correlation structure between single nucleotide polymorphisms (SNPs) within a 10-Mb window and using a random subset of 10,000 unrelated Europeans from the UKB as linkage disequilibrium (LD) reference. For comparison, we used PLINK [28] to identify regional lead SNPs for genome-wide significant loci, and subsequently clumped variants with this lead SNP if they were located less than 10 Mb away and had $r^2 > 0.01$ with the index variant. Since GCTA-COJO accounts for long-range LD and interaction effects between variants, it tends to be more conservative, reporting fewer but more valid independent loci, we use it as primary method to identify the independent genomic risk loci.

Pathway analysis

We used MAGENTA (Meta-Analysis Gene-set Enrichment of Variant Associations) to conduct a pathway-wide association analysis [29]. MAGENTA implements gene set enrichment analysis (GSEA) [30] from across five databases to test a total of 3,224 pathways and provides GSEA p-values for both 95th percentile and 75th percentile cutoffs. We chose the latter option, as it provides more statistical power when analyzing highly polygenic diseases [29]. Biological pathways were considered suggestively significant if their GSEA marginal P value was less than 0.05.

Tissue and cell-type enrichment analysis

We applied LDSC to perform tissue and cell-type enrichment analysis for FFS. We first used dichotomized annotations and 1000 Genomes European reference panels to estimate annotation-stratified LD scores. Enrichment was then defined as the ratio of the percentage of heritability explained by variants in each annotated category versus the percentage of variants covered by that category. In addition to the 53 baseline annotations [27] for diverse genomic features as suggested in the LDSC user manual and GenoCanyon general functionality scores [31], two tiers of annotations of different resolutions were further considered in enrichment analyses: 1) GenoSkyline-Plus functionality scores [32] of seven broad tissue clusters (immune, brain, cardiovascular, muscle, gastrointestinal tract, epithelial, other) and 2) GenoSkyline-Plus functionality scores of 66 tissue and cell types. For comparison, we also used MAGMA [33] to perform the tissue enrichment analysis, where we used annotation data from 30 general tissues types and 54 specific tissue types (GTEx project. v.8) [34] as provided by the FUMA (Functional Mapping and Annotation) platform [35]. Bonferroni multiple-testing correction was applied for each tier of enrichment analysis, separately.

Genetic correlation

To investigate potential shared underlying molecular mechanisms, we applied GNOVA [36], an annotation-stratified genetic covariance analyzer, to test the genetic correlation between FFS and a wide range of traits. We extracted GWAS summary statistics without large sample overlap with UKB from the LD Hub (http://ldsc.broadinstitute.org/gwashare/), the FinnGen cohort (https://finngen.gitbook.io/documentation/data-download), the Philadelphia Neurodevelopmental cohort (https://www.med.upenn.edu/bbl/philadelphianeurodevelopmentalcohort.html), and other large GWAS consortiums as organized previously [37], retaining available summary data for 2,086 traits in total. A Bonferroni-corrected $p < 2.4 \times 10^{-5}$ (corrected for 2,086 tests) was considered significant. Specifically, we also tested the genetic correlation between hearing loss [38] and frailty, as a strong epidemiological association between these two has long been observed [39].

Mendelian randomization

Mendelian randomization (MR) analysis is widely used to explore the potential causal relations between phenotypic traits and health-related outcomes. For the traits that had significant genetic correlation with FFS, we further investigated their causal associations with FFS. Specifically, we used inverse variance weighted MR (IVW-MR) [40] as the initial approach since it usually provides greater power to detect potential causal relationships. For traits with significant causal associations with FFS based on the IVW-MR, we also used other MR approaches in sensitivity analyses, including MR PRESSO [41], MR-Egger regression [42], weighted median MR [40] and mode-based methods [43] (e.g., simple mode MR and weighted mode MR). The 37 independent leading SNPs were used as instrumental variables.

Replication GWAS

To evaluate the consistency of our GWAS discovery results in an independent sample, we used data from the HRS (http://www.nia.nih.gov/research/resource/health-and-retirement-study-hrs) to conduct replication analyses. HRS is a nationally representative longitudinal survey of individuals over age 50 in 23,000 households in the USA. We included individuals from Waves 8–13 (2006–2016) of the HRS, as these waves contained physical measurement data for calculating the frailty score. A subgroup of 15,567 study participants underwent genome-wide genotyping using Illumina's Human Omni2.5-Quad (Omni2.5) BeadChip. The current analysis was restricted to study

participants of genetically confirmed European ancestry. The quality control, imputation, post-imputation filtering, and association testing were similar to the one used in the discovery cohort. Specifically, for variants that were genome-wide significant in UKB GWAS but not available or with low quality in HRS, we selected the variant having the highest LD, with the target variant within a 10-Mb window as the proxy-variant.

Polygenic risk score analysis

Polygenic risk scores (PRS) quantify the inherited risk for an individual by aggregating information from GWAS summary statistics. Here we applied PRS-CS [44] to generate weights for each genetic variant based on our GWAS summary statistics and 1000 Genomes LD reference panel. PRS for each individual in the replicated dataset was then calculated as the weighted sum of the genetic variants. The genetic variants we used were the overlaps between the reference panel, UKB and HRS genetic data. We calculated both odds ratio (OR) per standard deviation (SD) and area under ROC curve (AUC) to evaluate the prediction performance of PRS after adjustments for age, sex and first 10 PCs in a logistic regression model, where we used the binary frailty phenotype (FFS > = 3 is classified as frailty) as the outcome during the PRS evaluation.

Statistical analysis

In our replication analysis, we not only evaluated the associations of individual SNPs in the HRS cohort, but also conducted a sign test to compare the leading SNPs in both the UKBB and HRS cohorts. Specifically, we employed a binomial sign test with the null hypothesis that the probability of having the same sign in both cohorts is 0.5. The significance threshold was set at 0.05. To better visualize the results of the PRS analysis, we divided the HRS population into 20 groups based on PRS quantiles and calculated the mean frailty scores within each group. We then plotted the mean frailty scores against PRS to easily visualize the correlation between them. All statistical analyses in this study, aside from the genetic analysis tools mentioned previously, were performed using R software version 3.5.

Results

Characteristics of participants

The discovery phase included 386,565 participants of European ancestry with complete data for frailty criteria from the UKB (mean age 57 years [SD 8], 208,481 (54%) were female). The distribution of the FFS (from 0–5) in the UKB participants was: 231,629 (60%), 110,651 (29%), 31,561 (8%), 9,564 (2%), 2,801 (1%), and 359 (~0%), respectively. A comparison of the basic characteristics among the non-frail, pre-frail, and frail people is summarized in Table 1. The replication phase included 9,720 HRS participants with complete data for the FFS. This population was older than the UKB cohort (mean age 73 years, [SD 7]), with over half ($n = 5{,}582$, 57%) being female. The distribution of the FFS (from 0–5) in the HRS was: 3,734 (38%), 2,948 (30%), 1,769 (18%), 891 (9%), 357 (4%), and 21 (~0%), respectively.

GWAS

In the GWAS analysis (Fig. 1), a total of 8,883,488 SNPs with a MAF greater than 0.01 were examined. The estimated SNP heritability (h2) for FFS based on these SNPs in our data was 0.062 ± 0.003. LDSC produced a genomic inflation factor (λ_{GC}) estimate of 1.37 with an intercept of 1.03 ± 0.01 prior to inflation correction (Supp. Figure 2), suggesting that the inflation was probably due to polygenic signals and unlikely to be confounded by population structure [27]. Using COJO as our primary method, we identified 37 independent novel risk loci for FFS (Supp. Table 1). We obtained similar results when utilizing a clumping approach in PLINK (Supp. Table 2). Of these 37 novel loci for FFS, 30 have been previously reported to be associated with other traits (Supp. Table 3) and 7 have not been associated with any other traits (Supp. Figure 3). Among these 7 loci without previously described associations, the top associated variants within each locus included two intergenic variants (rs12992177 [*AC017104.2*, *AC017104.4*] and rs72709800 [*RN7SKP120*, *TUSC1*], four in protein-coding genes, including one splicing variant (rs10986468 in *ARPC5L*), one exonic variant (rs28509789 in *C15orf39*), and two intronic variants (rs2044169 in *METTL16* and 17:61,736,108:TTTTG:T in *MAP3K3*); and the remaining variant rs2857597 located 500b downstream from *AIF1*.

Table 1 Basic characteristics in the UK Biobank

Characteristics	All ($n=386,565$)	Non-frail ($n=231,629$)	Pre-frail ($n=142,212$)	Frail ($n=12,724$)
Age (years), mean (SD)	56.9 (8.0)	56.6 (8.0)	57.2 (8.0)	58.5 (7.4)
Sex, (Female, %)	208,481 (54%)	119,427 (52%)	81,067 (57%)	7,942 (62%)
BMI, mean (SD)	27.4 (4.7)	26.6 (4.1)	28.3 (5.1)	31.3 (6.7)
Hypertension, n (%)	212,532 (55%)	121,716 (53%)	82,001 (58%)	8,815 (69%)
T2D, n (%)	29,670 (8%)	11,323 (5%)	15,017 (11%)	3,330 (26%)
Lipid medication, n (%)	66,937 (17%)	32,509 (14%)	29,741 (21%)	4,687 (37%)
Current smoking, n (%)	38,397 (10%)	19,472 (8%)	16,359 (12%)	2,566 (20%)
Previous smoking, n (%)	136,282 (35%)	80,199 (35%)	51,400 (36%)	4,683 (37%)
CAD, n (%)	34,829 (9%)	18,145 (8%)	14,505 (10%)	2,179 (17%)
AF, n (%)	20,278 (5%)	10,299 (4%)	8,577 (6%)	1,402 (11%)

T2D Type 2 diabetes; *CAD* Coronary artery disease; *AF* Atrial fibrillation

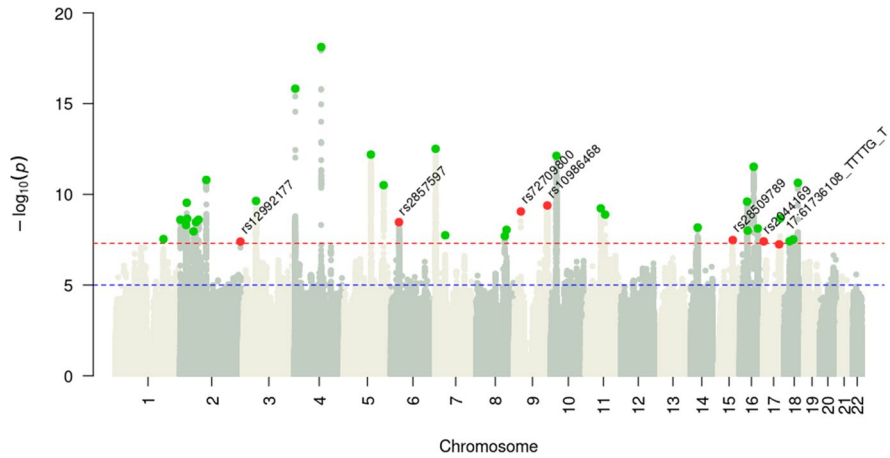


Fig. 1 Manhattan plot of the frailty GWAS in the UK Biobank. Manhattan plot for the discovery GWAS of frailty ($n=386,565$). Green dots indicate independent significant leading SNPs that have been reported to be associated with traits other than frailty; Red dots indicate independent significant leading SNPs that have never been reported before

Replication

In the replication phase, we analyzed 9,720 individuals from the HRS cohort. Of the 37 lead SNPs, 22 were eligible or well proxied by an eligible SNP in the HRS cohort after genetic QC. Of the 22 eligible SNPs, 18 were found to have consistent direction of effect in both UKB and HRS datasets, resulting in a highly significant P value of 0.00042 in the binomial sign test. Notably, three of these 18 SNPs retained significance in their individual associations with frailty when corrected for a 5% false discovery rate in the HRS (Fig. 2a). Taking the overlap between UKB genetic data and quality controlled HRS genetic data, we built a PRS based on 890,487 SNPs for 9,720 HRS individuals. After adjusting for age, sex and the first 10 PCs, the PRS was significantly associated with the frailty phenotype (OR per SD 1.27, 95% CI 1.22–1.31, $p=1.3\times10^{-11}$). The prediction performance of raw PRS was moderate with AUC being 0.57 (95% CI 0.56–0.59). When combined with age, sex and first 10 PCs, the prediction of frailty PRS achieved an AUC of 0.72 (95% CI 0.70–0.73) (Fig. 2b). The improvement in AUC when including the 10 PCs suggested that there may be sub-populations within the European British population that are captured by the PCs.

Gene set enrichment/pathway analysis

176 gene sets were marginally significantly ($P<0.05$) associated with the FFS using MAGENTA (Supp. Table 4), three of them remained significant after multiple testing correction, including response to drugs, multicellular organismal development, and aging. (Fig. 3a).

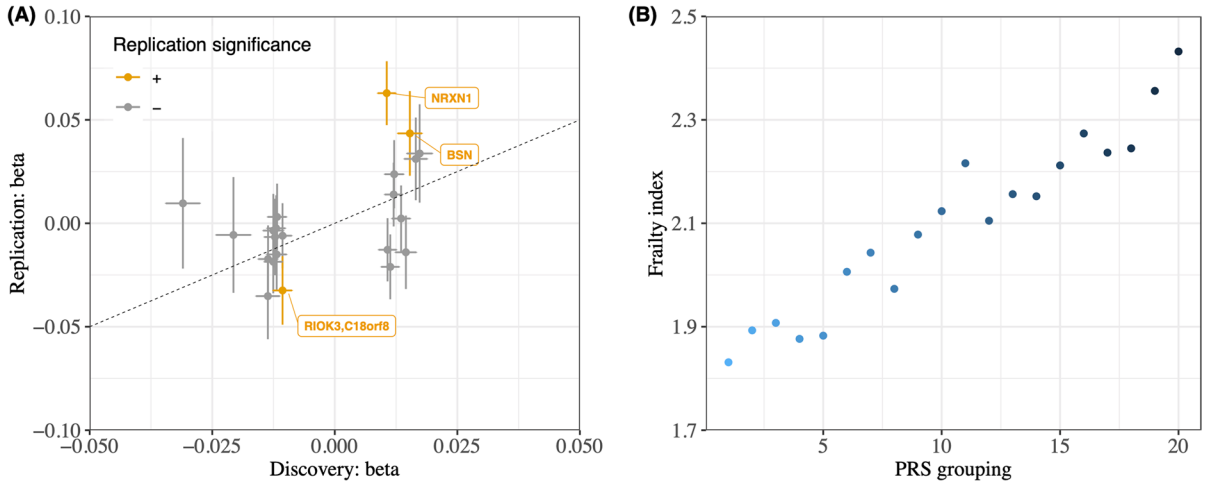


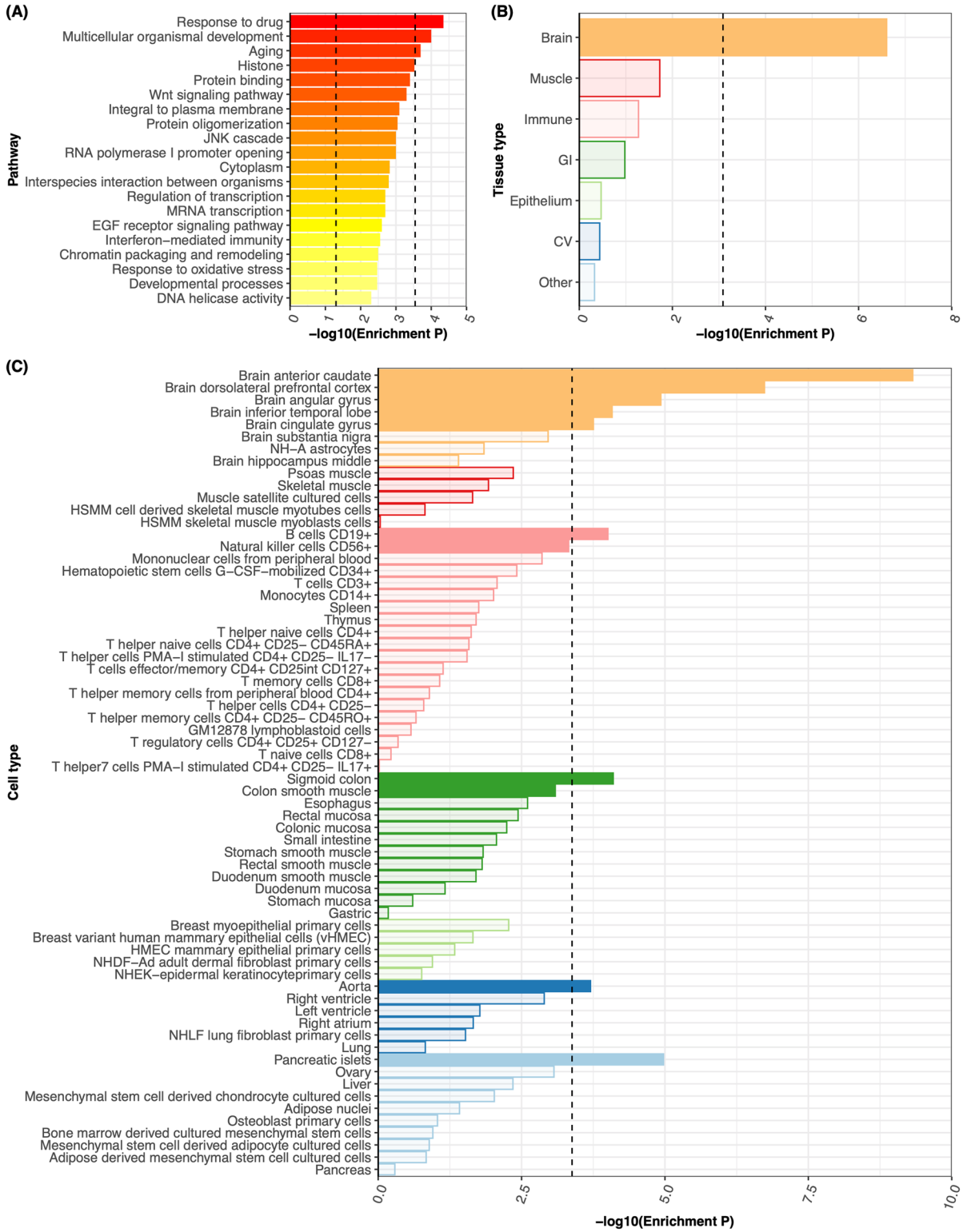
Fig. 2 Replication in the Health and Retirement Study. (**a**) We plotted the effect sizes of the SNPs identified in the discovery GWAS (UKBB) against their effect sizes in the replication GWAS (HRS). The points represent significant leading SNPs identified in the UKBB. The x-axis and y-axis depict the effect sizes of the SNPs in the UKBB and HRS, respectively. The colored points indicate SNPs that retained significance in the HRS. Specifically, out of the 22 SNPs in the plot, 18 had consistent directions of effects in both studies and three remained significant in HRS. (**b**) We visualized the association between the frailty phenotype and the frailty PRS in HRS by plotting the mean FFS in 20 groups, which were binned according to the percentile of the frailty PRS in HRS. The PRS was generated using the UKBB data. The plot shows a significant association between the frailty PRS and the frailty phenotype in the HRS cohort, further supporting that the genetic findings from our discovery GWAS are replicable

Tissue and cell-type enrichment

We used both LDSC and MAGMA to test whether genetic associations with FFS were enriched in human tissues and cell-types. Both LDSC and MAGMA indicated that brain tissues were significantly associated with frailty (Fig. 3b, Supp. Figure 4A, Supp. Table 5-8). Specifically, in the LDSC analysis, anterior caudate, dorsolateral prefrontal cortex, angular gyrus, inferior temporal lobe and cingulate gyrus in brain tissue were shown to be significantly enriched with frailty GWAS signals (Fig. 3c, Supp. Table 6). In the MAGMA analysis, frailty genetic associations were significantly enriched in cerebellar hemisphere, frontal cortex BA9, cerebellum, anterior cingulate cortex BA24 and the nucleus accumbens within the basal ganglia (Supp. Figure 4B, Supp. Table 8).

Genetic correlation

Of the 2,086 traits tested for genetic correlation with FFS, 591 had significant genetic correlations after Bonferroni correction (Supp. Table 9). The most significant of these were multisite chronic pain (genetic correlation (r_g)=1.079, $P=3.95\times10^{-264}$), BMI (r_g=0.714, $P=3.01\times10^{-196}$) and depressive symptoms (r_g=1.116, $P=3.23\times10^{-189}$). Among the other most interesting statistically significant genetic correlations were education attainment (r_g=-0.601, $P=5.36\times10^{-168}$), age of first birth (r_g=-0.692, $P=3.60\times10^{-95}$), insomnia (r_g=0.824, $P=7.82\times10^{-95}$), Attention-Deficit/Hyperactivity Disorder (ADHD, r_g=0.535, $P=6.05\times10^{-94}$), type 2 diabetes (r_g=0.416, $P=4.16\times10^{-72}$), smoking behavior (r_g=0.418, $P=1.14\times10^{-71}$), neuroticism (r_g=0.525, $P=4.52\times10^{-70}$), cognitive performance (r_g=-0.347, $P=5.40\times10^{-64}$), neurological diseases (0.484, $P=7.56\times10^{-57}$), and hypertensive diseases (0.376, $P=1.46\times10^{-56}$). Of the four types of hearing loss tested, both low frequency and low-to-medium frequency hearing loss were marginally significantly genetically correlated with FFS, while there was no evidence suggesting genetic correlation between high frequency hearing loss and FFS (Table 2). And possibly due to the small sample size of the available hearing loss GWAS, these genetic correlations do not pass the multiple testing correlation.


(A)
Pathway
Response to drug
Multicellular organismal development
Aging
Histone
Protein binding
Wnt signaling pathway
Integral to plasma membrane
Protein oligomerization
JNK cascade
RNA polymerase I promoter opening
Cytoplasm
Interspecies interaction between organisms
Regulation of transcription
MRNA transcription
EGF receptor signaling pathway
Interferon−mediated immunity
Chromatin packaging and remodeling
Response to oxidative stress
Developmental processes
DNA helicase activity
0 1 2 3 4 5
−log10(Enrichment P)
(B)
Tissue type
Brain
Muscle
Immune
GI
Epithelium
CV
Other
0 2 4 6 8
−log10(Enrichment P)
(C)
Cell type
Brain anterior caudate
Brain dorsolateral prefrontal cortex
Brain angular gyrus
Brain inferior temporal lobe
Brain cingulate gyrus
Brain substantia nigra
NH−A astrocytes
Brain hippocampus middle
Psoas muscle
Skeletal muscle
Muscle satellite cultured cells
HSMM cell derived skeletal muscle myotubes cells
HSMM skeletal muscle myoblasts cells
B cells CD19+
Natural killer cells CD56+
Mononuclear cells from peripheral blood
Hematopoietic stem cells G−CSF−mobilized CD34+
T cells CD3+
Monocytes CD14+
Spleen
Thymus
T helper naive cells CD4+
T helper naive cells CD4+ CD25− CD45RA+
T helper cells PMA−I stimulated CD4+ CD25− IL17−
T cells effector/memory CD4+ CD25int CD127+
T memory cells CD8+
T helper memory cells from peripheral blood CD4+
T helper cells CD4+ CD25−
T helper memory cells CD4+ CD25− CD45RO+
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T naive cells CD8+
T helper7 cells PMA−I stimulated CD4+ CD25− IL17+
Sigmoid colon
Colon smooth muscle
Esophagus
Rectal mucosa
Colonic mucosa
Small intestine
Stomach smooth muscle
Rectal smooth muscle
Duodenum smooth muscle
Duodenum mucosa
Stomach mucosa
Gastric
Breast myoepithelial primary cells
Breast variant human mammary epithelial cells (vHMEC)
HMEC mammary epithelial primary cells
NHDF−Ad adult dermal fibroblast primary cells
NHEK−epidermal keratinocyteprimary cells
Aorta
Right ventricle
Left ventricle
Right atrium
NHLF lung fibroblast primary cells
Lung
Pancreatic islets
Ovary
Liver
Mesenchymal stem cell derived chondrocyte cultured cells
Adipose nuclei
Osteoblast primary cells
Bone marrow derived cultured mesenchymal stem cells
Mesenchymal stem cell derived adipocyte cultured cells
Adipose derived mesenchymal stem cell cultured cells
Pancreas
0.0 2.5 5.0 7.5 10.0
−log10(Enrichment P)

◂**Fig. 3** Pathway and tissue enrichment. (**a**) The top 20 pathways associated with frailty were identified using pathway analysis based on our discovery GWAS. The left vertical dotted line represents a P-value of 0.05 for suggestive enrichment and the right vertical dotted line represents the Bonferroni-adjusted P-value for significant enrichment. We found that three pathways were significantly associated with frailty after Bonferroni correction. (**b**) and (**c**) show the results from tissue enrichment analysis based on LDSC. Specifically, (**b**) illustrates the enrichment results across 7 tissues, including brain, muscle, immune, gastrointestinal (GI), epithelium, cardiovascular (CV), and other tissues as annotated using GenoSkyline-Plus annotations. (**c**) provides a closer look at the stratified enrichment by sub-tissues or cell-types. In both panels (**b**) and (**c**), the vertical dotted line represents the Bonferroni-adjusted P-value for significant enrichment. The analysis revealed that brain tissues were significantly associated with frailty

Mendelian randomization

Of the 591 traits with significant genetic correlation with FFS, 8 could not be evaluated using MR analyses due to the lack of at least 10 valid instruments in the corresponding GWAS. Of the 583 traits evaluated via IVW-MR, 24 were causally associated with FFS after Bonferroni correction, including multisite chronic pain, education-related traits, joint disorders (e.g. rheumatism and carpal tunnel syndrome), depression (e.g. major depressive disorders, depressive symptom), interstitial lung disease related comorbidities, neurological diseases (e.g., nerve/nerve root/plexus disorders), endocrine/nutritional/metabolic diseases, respiratory diseases (e.g. asthma/chronic obstructive pulmonary disease, smoking: current or former smoker), father's age at death, obesity, and diabetes. (Fig. 4, Supp. Table 10). 17 of these causal associations remained significant when evaluated using the MR PRESSO. (Supp. Table 11).

Discussion

We report the largest-to-date GWAS of frailty, an important phenotype in aging research. Our study included over 380,000 individuals from two cohort studies and identified 37 novel susceptibility risk loci for frailty. Thirty of these newly found loci have been previously reported in GWASs of other traits, including obesity/BMI, lipids, coronary artery disease, hypertension, diabetes, and cancer. These results provide important confirmatory evidence for the associations of these traits with frailty found in observational and clinical studies [45–47]. Importantly, genetic correlation and MR analyses also revealed significant associations for pain, neuropsychiatric, cardiovascular, and inflammation-related traits, adding important evidence to support a causal link between these pathways and frailty.

We provide important new evidence related to the genetic underpinnings of frailty, an important phenotype in aging research that has been minimally investigated from a genomics perspective. Existing candidate-gene studies represented important first steps to identify genetic risk factors for frailty but are limited in scope, tend to yield inconsistent results, and many reported signals failed to reach statistical significance [12, 48]. The first GWAS study on frailty, conducted by Mekli et al. [14], was hampered by its relatively limited sample sizes ($n = 8532$) and the leading SNPs identified in their study were not replicable in the current study. Nevertheless, it is noteworthy that one of the two SNPs identified by Mekli et al. is related to brain development, synaptic plasticity, and cognition, which is consistent with our findings. A more recent GWAS conducted by Atkins et al. is more comparable to the current study [17], as they also used the UKBB as the discovery dataset. However, their study was restricted to older individuals, which resulted in a smaller sample size ($n = 164{,}610$) compared to this study. Additionally, the study by Atkins et al. used the FI instead of the FFS to define the frailty phenotype. The FI is a count of health-related problems, which is distinct from the physical frailty definition used in the current study by FFS. As a result of these differences, most of the loci identified by Atkins et al. were not present in our study. However, there was one notable exception: both studies identified a genetic locus located in the gene HTT, which has previously been linked to factors such as waist-hip ratio, LDL levels, and longevity [17].

Many novel loci with no reported associations are located at or close to protein-coding genes, pointing to novel pathophysiological pathways for frailty. rs10986469 is a splice site variant within *ARPC5L*, the gene that codes for Actin Related Protein 2/3 Complex Subunit 5 Like, a protein that regulates actin polymerization and branched actin networks. Similarly, rs2857597 is 500b downstream of *AIF1*, which encodes an actin-binding protein. *MAP3K3*, where the intronic variant 17:61,736,108:TTTTG:T resides, is a component of

Table 2 Genetic correlation between frailty and hearing loss

Hearing loss type	Correlation coefficient	Standard error	P
HML: HIGH – LOW	0.0031	0.005	0.53
HIGH: 4&8 kHz	0.0095	0.005	0.052
LOW: 0.5, 1, 2 kHz	0.0111	0.005	**0.025**
WHO: 0.5, 1, 2, 4 kHz	0.012	0.005	**0.010**

We highlight the *P* values passing significant threshold using bold formats

HML Patients with high frequency hearing loss without low frequency hearing loss; *HIGH* Patients with high frequency hearing loss; *LOW* Patients with low frequency hearing loss; *WHO* Patients with low-to-median hearing loss

protein kinase signal transduction cascades, mediating activation of *NF-kappa-B*, *AP1*, and *DDIT3* transcription regulators. *METTL16*, containing the intronic rs2044169, encodes a methyltransferase involved in RNA modification and gene expression. These genes have been linked to cancer and inflammation pathways [49], two groups of diseases with strong associations reported in observational studies [50].

Important to note is the relationship of frailty with the central nervous system, observed when using different, albeit complementary, analytical tools. Our tissue and cell-type enrichment analyses revealed that the genomic regions where frailty-associated SNPs are mapped, as determined by LD, are more likely to exhibit higher functional expression in brain tissues compared to other tissues. In addition, Genetic correlation analyses indicated a significant correlation between frailty variants and both neurological (especially cognitive decline) and psychiatric (depression, insomnia, ADHD, and neuroticism) diseases, with Mendelian randomization further implying the potential causality. These genetic findings are aligned with the results of existing cognitive and neuroanatomical studies showing that frailty is an early predictor of dementia and Alzheimer disease and is associated with reduced total brain volume, reduced gray matter volume, and increased cortical brain infarcts. [51] Our results provide important new evidence supporting these connections between frailty and disease involving the central nervous system. The specific underlying mechanisms are not yet fully understood, but previous research has identified shared biological pathways between frailty and cognitive impairment [52]. A more recent study found that the association between frailty and cognitive function persisted even after adjusting for potential confounders, suggesting that other mechanisms may be involved [53]. Further research is needed to fully understand the underlying mechanisms.

Aging research is increasingly interested in identifying biological pathways and therapeutic targets involved

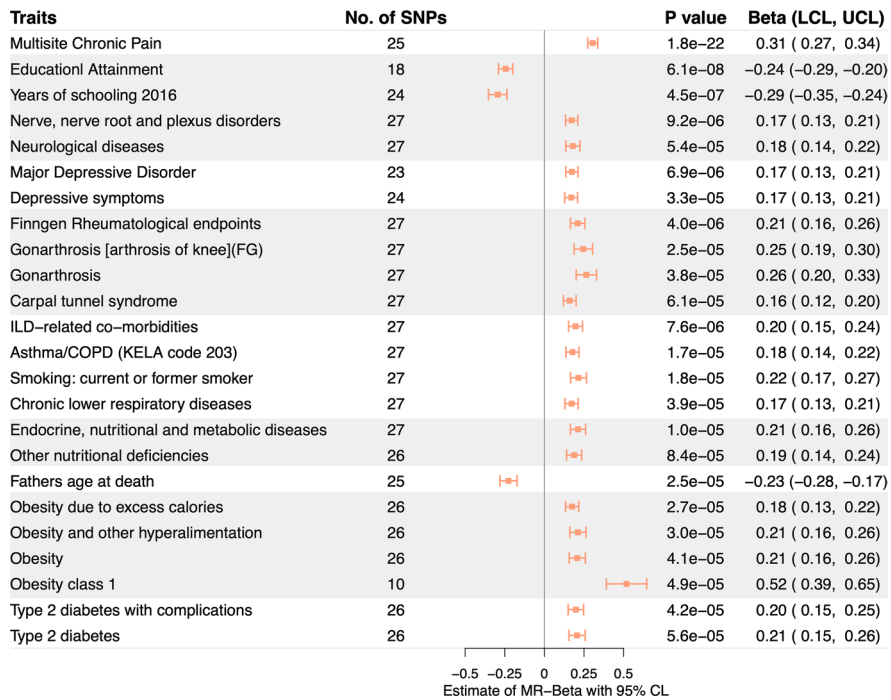

Fig. 4 Mendelian randomization analysis estimates. Effect sizes (beta) and 95% confidence intervals of the associations between FFS and significantly causally associated traits are provided (based on MR-IVW method)

in resilience rather than risk of disease [54]. This notion is particularly important for traits like frailty, that capture a person's general functional status and likely lie downstream in the causal pathway of several different specific diseases. Our study provides important novel results on this front, including the identification of genetic loci for frailty known to associate with intelligence as well as protective causal associations with years of schooling and educational attainment using Mendelian Randomization analyses. These causal associations are particularly important, as prior observational studies could not differentiate whether educational phenotypes constitute a true causal protective factor or a proxy for better health and socioeconomic status. Akin to cognitive reserve as a protective factor for dementia, these findings support the concept of "functional reserve" as a protective factor against frailty: it is possible that prolonged exposures to certain beneficial exposures, in this case educational activities, will improve a person's overall physical status resulting in a delay or avoidance of frailty.

Our study features many strengths, which include a large sample size of middle- and older-aged participants in our discovery and replication cohorts. We utilize the FFS, a physical model of frailty that can be easily assessed in the clinic, has been validated across multiple studies and populations [55], but has not yet been utilized to define frailty in published GWAS. A limitation of our study is the inclusion of only European-ancestry individuals. Participants of the UKB are also healthier and less socioeconomically deprived than the average population and thus do not reflect frail individuals who tend to be of low socioeconomic status and/or ethnic minorities [56]. In addition, many SNPs significantly associated with frailty in the UKB were not able to be replicated in HRS. This discrepancy may be due to certain leading SNPs being removed during quality control, or the proxy SNPs used in HRS not having sufficient power to reach statistical significance. Also, it is important to note that much of the variations in frailty are non-genetic, and various population-specific factors—both genetic and non-genetic—can affect the outcome. The small sample size of HRS also resulted in a heritability estimate with large uncertainty in the replication GWAS. Despite these limitations, three significant loci were replicated, and a PRS of all associated loci demonstrated good prediction of frailty status in HRS. While we have identified many possible causal relations between frailty and common diseases/traits using multiple MR methods, it is important to note that MR is an epidemiological tool and further experimental validation is necessary to confirm these findings. Contributions to frailty from epigenetics or rare variants (MAF < 0.01) should also be considered in future studies.

In conclusion, the genetic architecture of frailty is complex. Identification of individuals with a genetic predisposition to frailty provides an opportunity for the prevention and screening of frailty earlier in life and can inform clinical strategies in a myriad of specialties, from cardiology to oncology, to identify at-risk populations. Increasing efforts to address diabetes, obesity, and blood pressure, preventable and modifiable diseases, in midlife and later life may reduce the burden of frailty in our aging society.

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Data availability The UKBB data are available through the UK Biobank Access Management System. The HRS data are accessible on dbGap with accession number phs000428.v2.p2. A reporting summary for this article is available in the supplementary tables. The full GWAS summary statistics produced by this study are freely available on figshare (https://figshare.com/s/6683396c68807fe4e729).

Declarations

Web resources Finngen, https://www.finngen.fi/en/access_results

FUMA, https://fuma.ctglab.nl
GNOVA, https://github.com/xtonyjiang/GNOVA
HRS, http://www.nia.nih.gov/research/resource/health-and-retirement-study-hrs
LDhub, http://ldsc.broadinstitute.org/ldhub/
LDSC, https://github.com/bulik/ldsc
MAGENTA, https://software.broadinstitute.org/mpg/magenta/
PLINK, https://www.cog-genomics.org/plink/
PRScs, https://github.com/getian107/PRScs
UKBB, https://www.ukbiobank.ac.uk

Conflict of interest The authors declare that they have no conflict of interest.

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