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Original Article

Investigating the shared genetic architecture of osteoarthritis and frailty: a genome-wide cross-trait analysis

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Abstract: Observational studies suggest a link between osteoarthritis (OA) and frailty, but the shared genetic architecture and causal relationships remain unclear. We analyzed X-ray and ^{18}F-FDG PET/CT images in frail and non-frail individuals and conducted genetic correlation analyses using Linkage Disequilibrium Score Regression (LDSC) based on recent Genome-Wide Association Studies (GWAS) for OA and frailty. We identified pleiotropic single-nucleotide polymorphisms (SNPs) through Cross-Phenotype Association (CPASSOC) and Colocalization (COLOC) analyses and investigated genetic overlaps using Multi-marker Analysis of GenoMic Annotation (MAGMA). Transcriptome-wide association studies (TWAS) were conducted to analyze pleiotropic gene expression, and Mendelian Randomization (MR) was used to assess causal relationships between OA and frailty. Frail individuals showed more severe OA on X-ray (67% vs. 31%, $P \leq 0.01$) and higher SUVmax on ^{18}F-FDG PET/CT (4.1 vs. 3.6, $P < 0.05$) compared to non-frail individuals. Genetic correlation between frailty and OA was significant (rg = 0.532, P = 4.230E-88). Cross-trait analyses identified 42 genomic loci and 138 genes shared between the conditions. COLOC analysis revealed 2 pleiotropic loci, while TWAS identified 27 significant shared genetic expressions in whole blood and musculoskeletal tissue. Bidirectional MR indicated that OA increases the risk of frailty (IVW: beta: 0.13, P = 1.52E-08) and vice versa (IVW: beta: 0.73, P = 1.66E-04). Frail individuals exhibit more severe imaging features of OA. The shared genetic basis between OA and frailty suggests an intrinsic link, providing new insights into the relationship between these conditions.

Keywords: X-ray, ^{18}F-FDG PET/CT, genome-wide cross-trait analysis, osteoarthritis, frailty

Introduction

Osteoarthritis (OA) is a chronic disease characterized by degenerative changes in joint cartilage, affecting approximately 350 million people worldwide [1]. In the United States, about 23% of adults are diagnosed with osteoarthritis, and the incidence increases significantly with age. Frailty is a multisystem functional decline syndrome characterized by increased vulnerability to stressors [2] and the prevalence of frailty is about 10-15% in people aged 60 and above [3].

As a degenerative disease, OA can lead to a reduced ability to adapt to external stressors, resulting in adverse outcomes such as organ damage and an increased risk of death [4, 5]. In the United States, the treatment and care of OA alone generates a financial expenditure of $27 billion [6]. Early prevention and treatment of OA, as well as identifying patients at high risk of severe pain, are very important. Epidemiological studies indicated that symptomatic OA and other chronic pain are associated with an increased risk of frailty. This connection is likely due to common mechanisms including chronic inflammation, neuroinflammation, and endocrine dysregulation [7]. On the other hand, the condition arises from the chronic pain, inflammation, and restricted activity associated with OA, which in turn contribute to a reduction in physical function and a heightened risk of frailty [8]. Despite numerous studies supporting the association between OA and frailty, some results remain inconsistent. In a cross-sectional study, Song et al. found a significant association between knee OA and frailty [9] and frailty were related to the severity of pain of OA [10]. A UK Biobank analysis indicated that those with OA had significantly higher relative risk ratios for pre-frailty and frailty compared to those without OA [11]. However, some studies have found no link between musculoskeletal pain and frailty [12]. The comorbidity rate of OA and frailty is higher in older populations, while this association may be less significant in younger groups. What is more, research in older Chileans found that frailty was significantly more prevalent among women with OA than men [13]. Lifestyle factors like sedentary behavior can also been shown to increase the risk of physical frailty [14]. Overall, the results of observational studies are prone to confounding factors, and the true association between the two still requires further exploration.

With the rapid progress of GWAS, the relationship between genetic background and traits has gradually been revealed. Previous studies using MR have found that frailty increases the risk of developing mental disorders [15, 16]. But whether the related genetic variations affect the occurrence and development of OA remains unknown.

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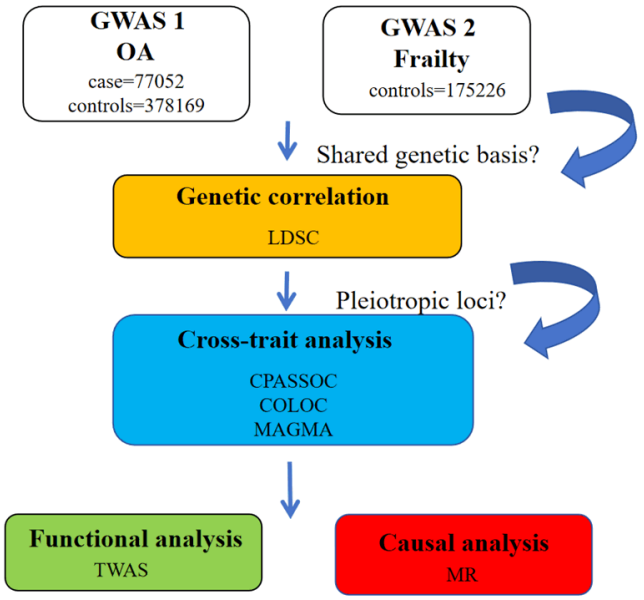

Figure 1. Overview of research of shared genetic architecture between OA and frailty.

Given the importance of early diagnosis of OA, it is crucial to identify potential modifiable risk factors. The frail population, due to its prevalence and association with various health outcomes, is increasingly being recognized as a potential target. What is more, imaging plays a crucial role in the diagnosis and management of OA. X-ray is the most commonly used technique, capable of showing joint space narrowing, osteophyte formation, subchondral bone sclerosis, and cystic changes, which provide important support for early diagnosis, disease progression assessment, and treatment decision-making [17]. Additionally, ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) imaging was widely used, which offers high image resolution and/or functional characterization at the early disease stage [18].

Therefore, in this study we mainly used post-GWAS analysis methods to investigate their genetic structure, including: (1) we conducted a clinical cross-sectional study to analyze X-ray and ^{18}F-FDG PET-CT images of OA in frail and non-frail individuals, observing the differences between the two groups, (2) analyzing the genetic correlation between OA and frailty using LDSC, (3) identifying shared genetic loci and genes between OA and frailty through cross-trait analysis, (4) examining the expression of shared genes using TWAS, (5) analyzing the causal relationship between hypothyroidism and frailty using MR.

Methods

Data preparation

Frailty can be assessed clinically using the Frailty Index Score (FI) based on an individual's extensive health deficits. The frailty assessment is conducted using a 32-item frailty index (FI), which includes various characteristics such as comorbidities, physical function, disability, depression, and cognition. It is calculated by summing the existing health deficits and dividing the result by 32. Therefore, the FI is a continuous variable ranging from 0 to 1, with higher values indicating a greater degree of frailty [19]. We conducted frailty index assessments and collected corresponding imaging data for 31 frail and 34 non-frail patients with osteoarthritis at the Second Xiangya Hospital of Central South University.

The OA X-ray grading is as follows: Grade 0 represents a normal knee joint; Grade I indicates suspected joint space narrowing with possible osteophyte formation; Grade II shows mild joint space narrowing with noticeable small osteophytes; Grade III is characterized by definitive joint space narrowing with moderate osteophyte formation, mild subchondral bone sclerosis, and possible knee joint deformities such as varus, valgus, or flexion deformities; and Grade IV involves severe joint space narrowing, extensive osteophyte formation, significant subchondral bone sclerosis, and pronounced knee joint deformities [20]. For osteoarthritis classified as Grade II or below, we labeled it as mild with a value of 0; for grades above II, it was labeled as severe with a value of 1.

Inclusion criteria: (1) Patients diagnosed with both osteoarthritis and frailty; (2) Availability of comprehensive clinical baseline data and frailty assessment scales; (3) Availability of complete imaging data, including X-ray and PET scans. Exclusion criteria: (1) Presence of severe comorbidities such as end-stage heart disease, renal failure, or severe mental disorders; (2) Existence of other joint diseases, such as rheumatoid arthritis (RA), gout, or any other non-osteoarthritis-related joint conditions. All participants provided written informed consent.

A recent meta-analysis of GWAS involving 175226 European individuals from the UK Biobank and Swedish Twin Gene provided summary statistics for FI. The sample size for the GWAS of OA includes 77052 cases of European ancestry and 378169 controls of European ancestry (https://www.ebi.ac.uk/gwas/studies/GCST007093). Both are derived from public databases. Based on the European 1000 Genomes Project, we removed SNPs with duplicate rsid numbers to ensure consistency in the major alleles between the two sources (**Figure 1**).

Genetic correlation

Genetic correlation analysis was conducted using linkage disequilibrium score regression (LDSC), which measures the shared genetic effects across the genome for two traits, represented by heritability (h^2) [21] and genetic correlation (rg) [22]. A *p*-value less than 0.05 indicates a significant correlation between the two variables.

Cross-trait analysis

Cross-trait meta-analysis (CPASSOC) combines summary data from multiple correlated traits obtained from GWAS

Table 1. The comparison between frail and non-frail individuals

Parameters	Frail	Non-Frail	*P*
Age	79.27 ± 2.74	79.67 ± 2.90	0.31
Sex (M/F)	15/16	17/15	0.71
FI	0.053 ± 0.027	0.024 ± 0.022	2.09E-06***
Severe OA	20	10	0.01*
Mild OA	11	22	
SUVmax	4.1 (3.8, 4.2)	3.6 (3.4, 3.8)	0.03*

The severe OA is defined as the OA X-ray grading < Grade 2, and the Mild OA is defined as the OA X-ray grading ≥ Grade 2. *** presents $P < 0.001$, * presents $P < 0.050$.

to identify genetic variants linked to at least one trait, improving test efficacy and sample size [22]. Significant pleiotropic SNPs showed genome-wide significance with $P_{CPASSOC}$ = 5E-08 for paired traits and $P_{single\ trait}$ = 1E-03 for single traits. This study proposed that meta-analysis significance with P < 5E-08 and trait-specific significance from 5E-08 to 1E-03 suggests novel shared loci between two traits.

Further investigation is needed to determine if two traits are caused by the same or different genetic variants in close proximity. Colocalization analysis (COLOC) using a Bayesian algorithm generated posterior probabilities for five hypotheses about causal variants in a genomic region [23]. Summary data for variations within 5 Mb of the index SNP were analyzed to compute probabilities for H4 (PPH4) and H3 (PPH3), with PPH4 greater than 70% indicating significant genetic variation associated with both traits.

The functional mapping and annotation (FUMA) [24] tool annotated pleiotropic SNPs based on their physical location. The Multi-marker Analysis of GenoMic Annotation (MAGMA) [25] tool was used for gene and gene-set analysis, incorporating linkage disequilibrium between SNPs. Genes within 500 kb of each candidate SNP were mapped and prioritized if they were in linkage disequilibrium with genome-wide significant SNPs. The intersection of genes identified by MAGMA and CPASSOC was considered for further analysis.

Functional analysis

Genetic variations affecting complex traits often regulate gene expression, known as functional genes. The transcriptome-wide association study (TWAS) [26] algorithm utilizes these reference individuals to estimate gene expression patterns. These patterns are then extrapolated to a larger population based on SNP genotypes. Predictive models from musculoskeletal and whole blood tissues associated with the musculoskeletal system served as reference templates. TWAS enables the identification of key genetic factors that may influence complex traits, enhancing our understanding of the genetic architecture of complex traits and diseases.

Causality

Finally, we used in order to infer putative causal relationships between OA and frailty. Mendelian Randomization (MR) [27] is an epidemiological research method that uses genetic variations as instrumental variables to assess causal relationships. Because genetic variations are randomly distributed in the general population and remain unchanged throughout the life course, the MR method is less likely to be biased by confounding factors and reverse causality. To further investigate the causal relationship between OA and frailty, we conducted a bidirectional MR with the two traits separately as exposure and outcome.

Statistical analysis

All statistical analysis was performed using SPSS statistical software version 26 (IBM Corporation, Armonk, New York). Descriptive statistics were computed to summarize the data. Non-normal variables were presented by medians with interquartile range, and categorical or ordinal variables were presented as frequency (percentage). Differences between the two groups were compared using the Mann-Whitney U test for non-normally distributed continuous variables. The χ^2 test was used for comparing groups for categorical variables. A 2-sided *P* value < 0.05 was considered statistically significant.

Result

Clinical analysis

There was no significant difference in the number of mild OA cases, age, or sex distribution between the two groups (P = 0.82 and P = 0.71, respectively). However, frail individuals had a significantly higher fatigue index (0.053 ± 0.027) compared to non-frail individuals (0.024 ± 0.022), with a highly significant *p*-value (P = 2.09E-06***). In the frail individuals, 67% (n = 20) frail individuals were diagnosed as severe OA, 33% (n = 11) frail individuals were diagnosed as mild OA on the X-ray image. While, only 31% (n = 10) non-frail patients were diagnosed as severe OA, 69% (n = 22) non-frail patients were diagnosed as mild OA. Results showed that a significant difference existed between frail and non-frail individuals on the X-ray image (P = 0.01*). And the SUVmax of frail individuals was 4.1 (3.8, 4.2), which is higher than the non-frail individuals [SUVmax: 3.6 (3.4, 3.8), P = 0.03*] (**Table 1**). The legend of frail and non-frail individuals is shown in **Figure 2**.

Genetic correlation

The h^2 of OA was 0.046, and the h^2 of frailty is 0.108. Individuals with frailty are more likely to develop OA. The genetic correlation between OA and frailty was significantly positive (rg = 0.532, P = 4.230E-88).

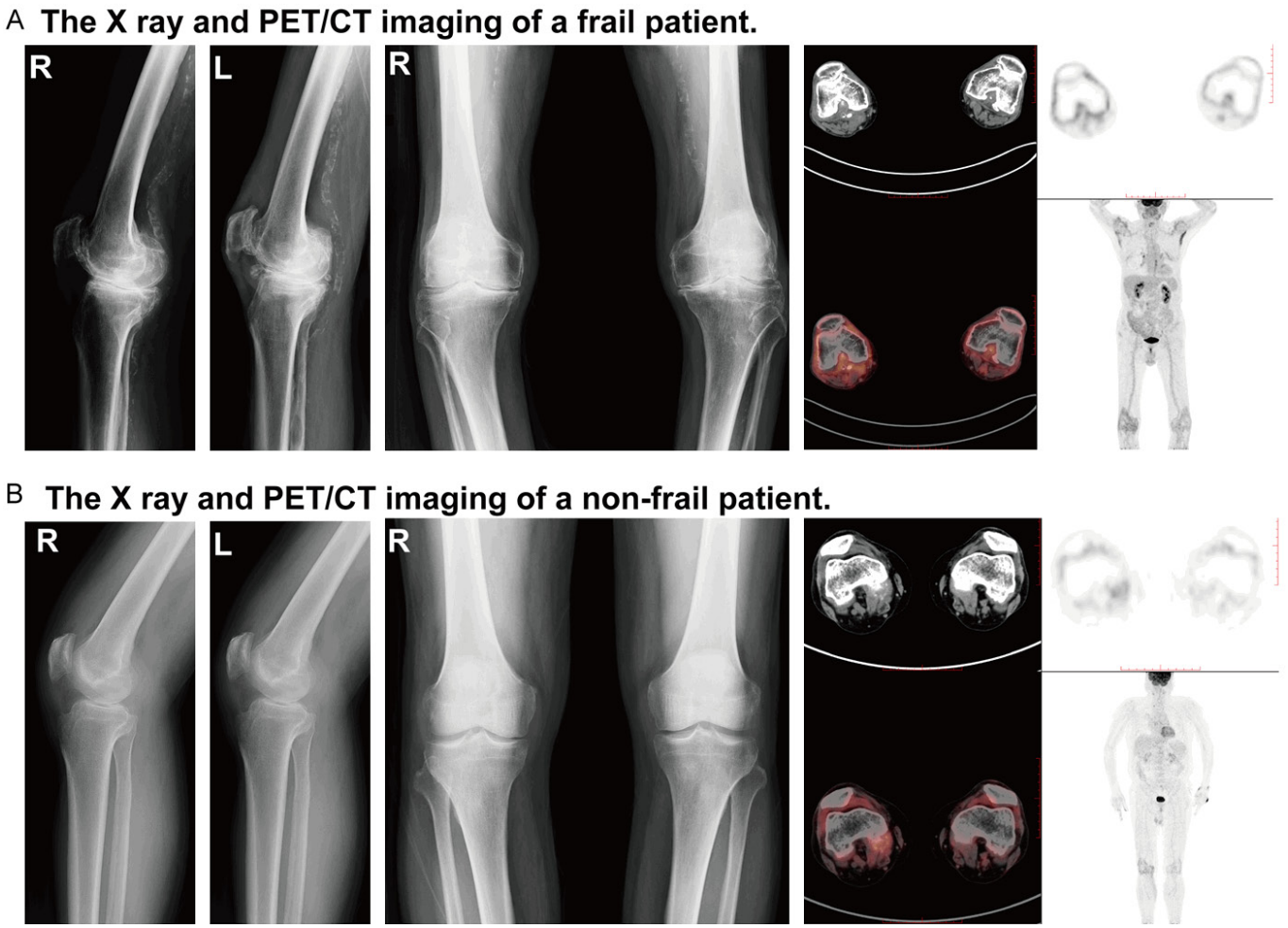

Figure 2. Legend of X-ray and PET/CT images of frail and non-frail patients. A. The left lateral, right lateral and orthopantomograms on X-ray and PET/CT images of a frail patient (male, 78 years old) defined as severe OA on X-ray images, with a high number of osteophyte formations, severe joint space narrowing, significant subchondral osteosclerosis and significant bony deformities of the knee joint. The ^{18}F-FDG uptake was significantly increased (the SUVmax of the right keen was 4.4); B. The left lateral, right lateral and orthopantomograms on X-ray and PET/CT images of a non-frail patient (male, 74 years old) defined as mild OA, which showed bilateral tibial intercondylar eminences becoming pointed, few osteophytes at the femoral condylar edges and patellar edges, and bilateral tibiofemoral joint spaces becoming slightly narrower medially. The ^{18}F-FDG uptake was mildly increased (the SUVmax of the right keen was 3.3).

CPASSOC

Through meta-analysis, we identified a total of 178 pleiotropic SNPs. These SNPs satisfied the criteria of having P < 0.001 in the GWAS of OA and frailty, as well as P < 5E-08 in the meta-analysis results (Supplementary Table 1). The most significant SNP identified was rs17612712, located on chromosome: position (chr: bp): 32615945, with a *P*-value of 1.217E-19. The second most significant SNP was rs543993279, with a *P*-value of 1.987E-15. Additionally, the study discovered 23 novel SNPs associated with OA and 123 novel SNPs in frailty (5E-08 < P < 0.001).

COLOC

We used the FUMA platform to annotate the CPASSOC results, identifying 42 loci (Supplementary Table 2). Since the CPASSOC algorithm primarily employs meta-analysis, we conducted colocalization analysis and found that 2 loci had PPH4 > 70%. One of these loci had a topSNP of rs11599313, with P = 3.277E-10 and PPH4 = 0.978, corresponding to a total of 17 genes. The second locus had a topSNP of rs34811474, with P = 2.28E-11 and PPH4 = 0.903, corresponding to 2 genes, including *ZCCHC4* and *ANAPC4* (**Table 2**).

MAGMA

A total of 19246 genes were found in the MAGMA analysis, among which 4929 genes showed significance in both OA and frailty (Supplementary Table 3). Among them, 138 genes overlapped with the annotated findings from FUMA. After Bonferroni correction, there were 108 genes significantly shared with both OA and frailty (Supplementary Table 4). With Ubiquinol-Cytochrome c Reductase Complex Assembly Factor 1 (*UQCC1*) being the most significant, which is located on chr: bp: 20:33840369~34049944 with a *P*-value of 5.05E-13. It is a key mitochondrial protein involved in the assembly of the ubiquinol-cytochrome c reductase complex, essential

Table 2. Results from colocalization analysis for each pleiotropic locus identified from CPASSOC

GenomicRisk loci	TopSNP	Chr	Start	End	PPH4	Gene clumped in this locus
11	rs11599313	3	49734229	50250837	0.98	MST1 IP6K1 UBA7 TRAIP RBM6 RBM5 GNAT1 MON1A CAMKV MST1R GMPPB CDHR4 SEMA3F RNF123 AMIGO3 FAM212A CTD-2330K9.3
17	rs34811474	4	25342606	25408838	0.90	ZCCHC4 ANAPC4

for maintaining cellular energy metabolism and mitochondrial function [28]. RNA Binding Motif Protein 5 (*RBM5*) was the second significant gene which an edited enzyme responsible for the reversible interconversion of 17-hydroxy and 17-ketosteroids. It is located on chr: bp: 6:33122419~33224608, with a *P*-value of 1.61E-19. XK-related protein 6 (*XKR6*) plays a crucial role in the process of apoptosis by regulating phospholipase activity and promoting the externalization of phosphatidylserine, which marks the occurrence of cell apoptosis. It is located on chr: bp: 8 10703555~11108875, with a *P*-value of 1.61E-19.

TWAS

There were 83 TWAS-significant associations after Benjamini-Hochberg FDR correction for frailty were identified in the musculoskeletal tissue, the strongest expression-trait association was observed at *FAM212A* (P = 6.20E-09, P_{FDR} = 5.26E-05), which has previously been identified as a pleiotropic gene for frailty and insomnia [29]. 220 TWAS-significant associations for OA were identified after FDR correction in the musculoskeletal tissue (Supplementary Table 5; **Figure 3**), the strongest expression-trait association was observed at *UQCC1* (P = 2.89E-12, P_{FDR} = 2.42E-08), which was also the most significant gene found at the genetic level to be associated with both traits. We identified 15 TWAS-significant genes shared between frailty and OA in the musculoskeletal tissue. COLOC studies found that the PPH4 value of the loci which 7 genes located were greater than 90%. We also found 160 TWAS-significant genes for OA after FDR correction (Supplementary Table 5; **Figure 4**) in whole blood tissue and *SCAMP2* (P = 1.140E-12, P_{FDR} = 8.92E-09) was the gene most significantly expressed in the tissue, which encodes secretory carrier-associated membrane protein-2 [30]. The 64 TWAS-significant associations for frailty were identified after FDR correction and the strongest expression-trait association was observed at CHP1 (P = 2.89E-12, PFDR = 2.42E-08), which is related to inflammation and neuronal death [31]. The PPH4 value for the loci which can mapped 6 genes was found to be greater than 90% in COLOC studies. We also identified 12 TWAS-significant genes shared between frailty and OA in the blood tissue (**Table 3**).

MR

When OA was the exposure, based on the instrument variable selection criteria of P < 5E-08 and after clumping (clump_kb = 10000, clump_r^2 = 0.001), we obtained a total of 30 instrumental variables. The IVW method showed that genetically predicted higher OA was significantly associated with a higher frailty index (IVW: beta: 0.13, 95% CI: 1.09 to 1.20, P = 1.52E-08). The presence of significant heterogeneity was indicated by Cochran's Q statistics (P = 0.002), leading to the use of the random-effect IVW model to address this heterogeneity. Furthermore, both the MR-Egger intercept test suggested that horizontal pleiotropy was unlikely (P = 0.573). Conversely, when frailty was the exposure, there were 8 instrumental variables. The IVW method indicated frailty would increases the risk of developing OA (IVW: beta: 0.73, 95% CI: 1.42 to 3.05, P = 1.66E-04). We also used a random effects model to address the issue of heterogeneity in the results and the *P*-value obtained from the MR-Egger intercept test is greater than 0.05 (**Table 4**; **Figures 5**, **6**).

Discussion

In the clinical practice, we had observed that frail patients seemed obtained more severe imaging characteristics. Further studies confirmed that the characteristics of X-ray and ^{18}F-FDG PET/CT in frail individuals were more severe than non-frail individuals. To figure out the relationship between OA and frailty, post-GWAS analysis methods were used to investigate their genetic structure. This study provides strong evidence that OA and frailty share similar genetic variation mechanisms and exhibit significant genetic correlation, consistent with the high comorbidity observed clinically. The results from cross-trait meta-analysis suggest that the observational link may largely be explained by potential pleiotropic variants affecting both traits. In the SNP analysis results, most of the pleiotropic SNPs shared between OA and frailty we obtained were in the same direction. In genetic level anal-

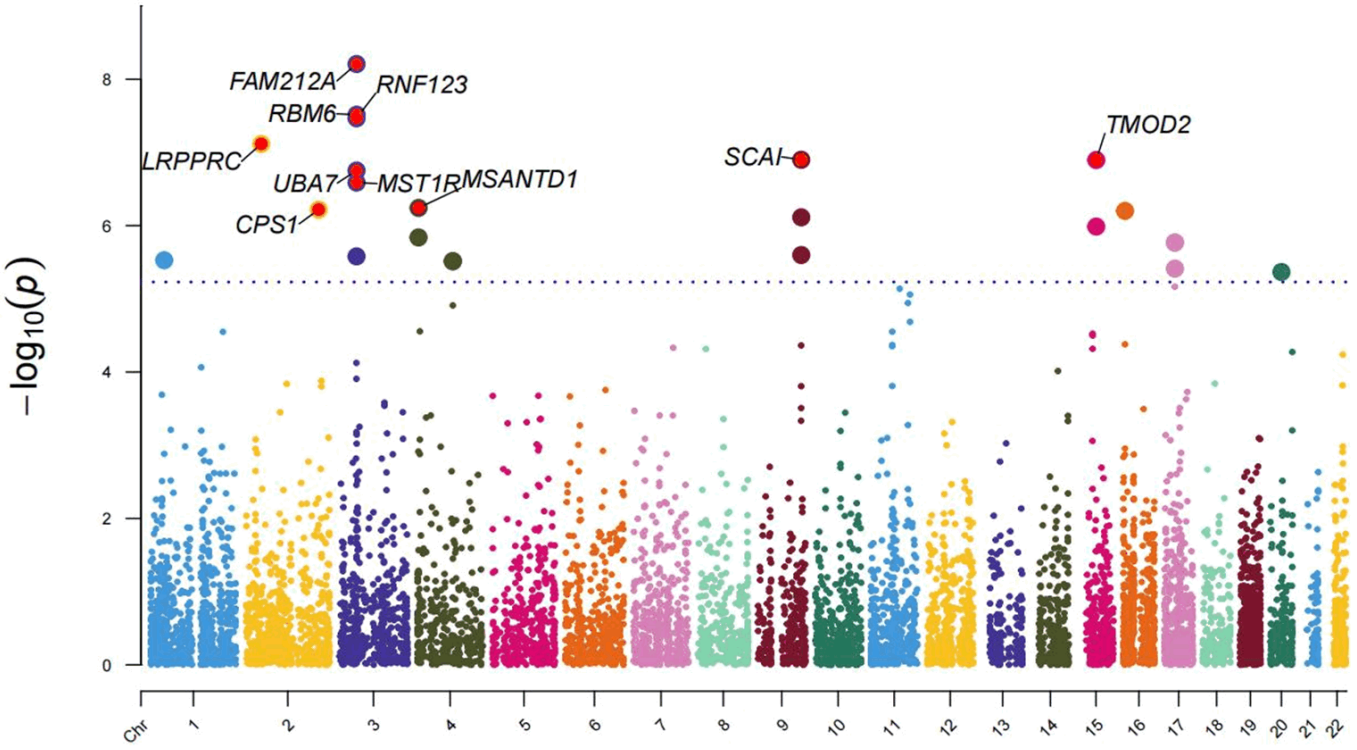

Figure 3. The Manhattan plot of the GWAS of OA. Results separately display the top ten significant genes detected by TWAS from OA and frailty.

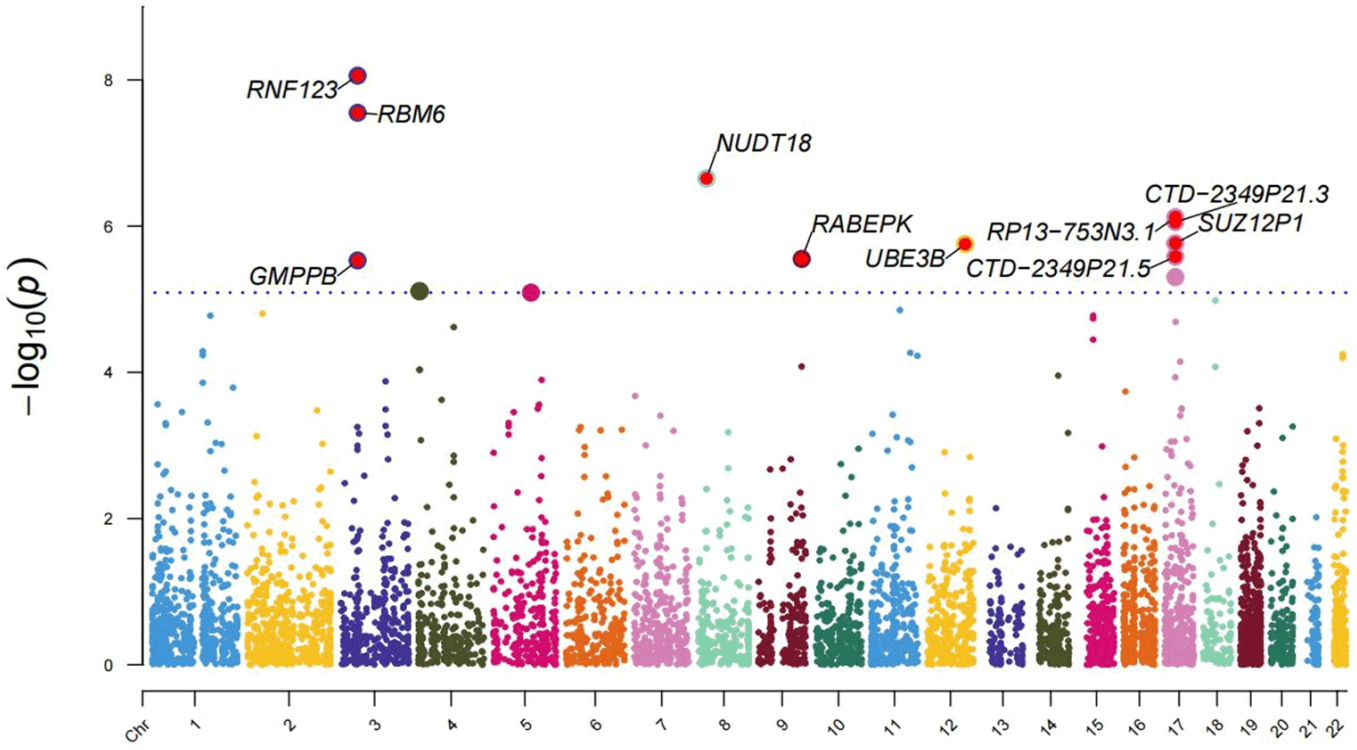

Figure 4. The Manhattan plot of the GWAS of frailty. Results separately display the top ten significant genes detected by TWAS from OA and frailty.

ysis, multiple methods indicate that *MST1* and *MST1R* gene variations are involved in the co-occurrence of both conditions. COLOC identified loci with significant results corresponding to a total of 19 genes, among which seven expression-trait associations were found. TWAS found that *MSTI* is significantly expressed in musculoskeletal

Table 3. Results of significant shared gene between OA and frailty detected by TWAS

ID	Panel	Frailty			OA		
		TWAS.Z.x	TWAS.P.x	TWAS.fdr.P.x	TWAS.Z.y	TWAS.P.y	TWAS.fdr.P.y
AMT	GTExv8.EUR.Whole_Blood	-3.64	2.68E-04	4.01E-02	-4.18	2.91E-05	4.55E-03
CACYBP		3.72	1.97E-04	3.27E-02	4.78	1.77E-06	7.69E-04
CRLF3		4.73	2.29E-06	1.81E-03	3.70	2.16E-04	1.82E-02
GMPPB		4.57	4.92E-06	3.25E-03	4.89	9.84E-07	4.88E-04
MST1		-4.21	2.58E-05	8.82E-03	-4.04	5.40E-05	6.89E-03
MST1R		-4.37	1.25E-05	5.83E-03	-5.56	2.75E-08	4.30E-05
PABPC4		-3.86	1.14E-04	2.48E-02	-3.39	7.00E-04	4.00E-02
RBM6		-5.45	4.91E-08	1.95E-04	-6.15	7.97E-10	2.08E-06
SMG1P5		-3.54	3.95E-04	4.92E-02	-3.71	2.05E-04	1.78E-02
SUZ12P1		4.69	2.77E-06	2.00E-03	4.06	4.90E-05	6.65E-03
UBA7		-5.14	2.80E-07	4.24E-04	-5.45	5.05E-08	6.59E-05
ZCCHC4		3.56	3.74E-04	4.78E-02	3.82	1.33E-04	1.32E-02
CACNG4	GTExv8.EUR.Muscle_Skeletal	-3.74	1.87E-04	2.83E-02	-3.25	1.14E-03	4.54E-02
CTD-2349P21.3		4.79	1.71E-06	9.07E-04	3.87	1.08E-04	9.14E-03
FAM212A		5.81	6.20E-09	5.26E-05	4.43	9.62E-06	1.67E-03
FOXP2		-3.54	3.93E-04	4.48E-02	-3.47	5.19E-04	2.59E-02
GMPPB		4.70	2.63E-06	1.24E-03	4.76	1.90E-06	4.68E-04
MDFIC		-4.07	4.67E-05	1.00E-02	-3.36	7.67E-04	3.49E-02
MST1R		5.15	2.58E-07	2.74E-04	5.96	2.47E-09	4.14E-06
PPP1R13B		-3.54	3.96E-04	4.48E-02	-3.91	9.09E-05	8.27E-03
RBM6		-5.54	3.05E-08	9.64E-05	-6.10	1.06E-09	2.49E-06
RHOA		3.84	1.24E-04	2.24E-02	4.99	5.91E-07	2.75E-04
RNF123		5.52	3.41E-08	9.64E-05	5.68	1.36E-08	1.27E-05
SUZ12P1		4.79	1.70E-06	9.07E-04	3.87	1.10E-04	9.21E-03
UBA7		5.22	1.77E-07	2.14E-04	4.16	3.13E-05	4.01E-03
ZCCHC4		3.53	4.19E-04	4.68E-02	3.90	9.71E-05	8.47E-03
ATAD5		-4.50	6.83E-06	2.41E-03	-3.68	2.31E-04	1.43E-02

Table 4. MR results of causal effects between OA and frailty

Exposure	Outcome	Method	nSNP	b	SE	pval	OR (95% CI)
OA	Frailty	Weighted median	30	0.13	0.03	2.66E-06	1.13 (1.07 to 1.20)
OA	Frailty	Inverse variance weighted	30	0.13	0.02	1.52E-08	1.14 (1.09 to 1.20)
Frailty	OA	Weighted median	8	0.66	0.16	5.85E-05	1.93 (1.40 to 2.67)
Frailty	OA	Inverse variance weighted	8	0.73	0.19	1.66E-04	2.08 (1.42 to 3.05)

CI, confidence interval; nSNP, n single nucleotide polymorphism; OR, Odds ratio.

tissues, while *MST1* (mammalian sterile 20-like kinase 1) and *MST1R* (macrophage stimulating 1 receptor) are significantly expressed in blood. *MST1* and *MST1R* genes have been previously identified as associated with OA in earlier studies. The *MST1* gene is highly expressed in OA patients. Inhibiting *MST1* can suppress apoptosis, inflammation, and ECM degradation by promoting Parkin-mediated mitophagy and the Nrf2-NF-kB axis [32]. XMU-MP-1 is a selective MST1/2 inhibitor that has protective and therapeutic effects in a mouse OA model [33]. *MST1* is involved in regulating glucose uptake and mitochondrial function, thus, variations in this gene can lead to reduced energy production and increased oxidative damage [34]. Metabolic dysregulation and mitochondrial dysfunction are significant contributors to frailty [35]. In addition, *MST1* is a kinase associated with oxidative stress which can be activated under oxidative stress conditions and is involved in regulating cellular stress responses and cell death processes [36]. Oxidative stress contributes to cellular aging and frailty by damaging cells and tissues [37]. *MST1R* influences macrophage activity and cytokine production, playing a role in inflammatory responses, whose dysregulation can exacerbate inflammatory conditions, leading to tissue degeneration and frailty [38]. Further research is needed to confirm the observed expression patterns of *MSTI* and *MST1R* in musculoskeletal and blood tissues especially the patient suffers from both OA and frailty.

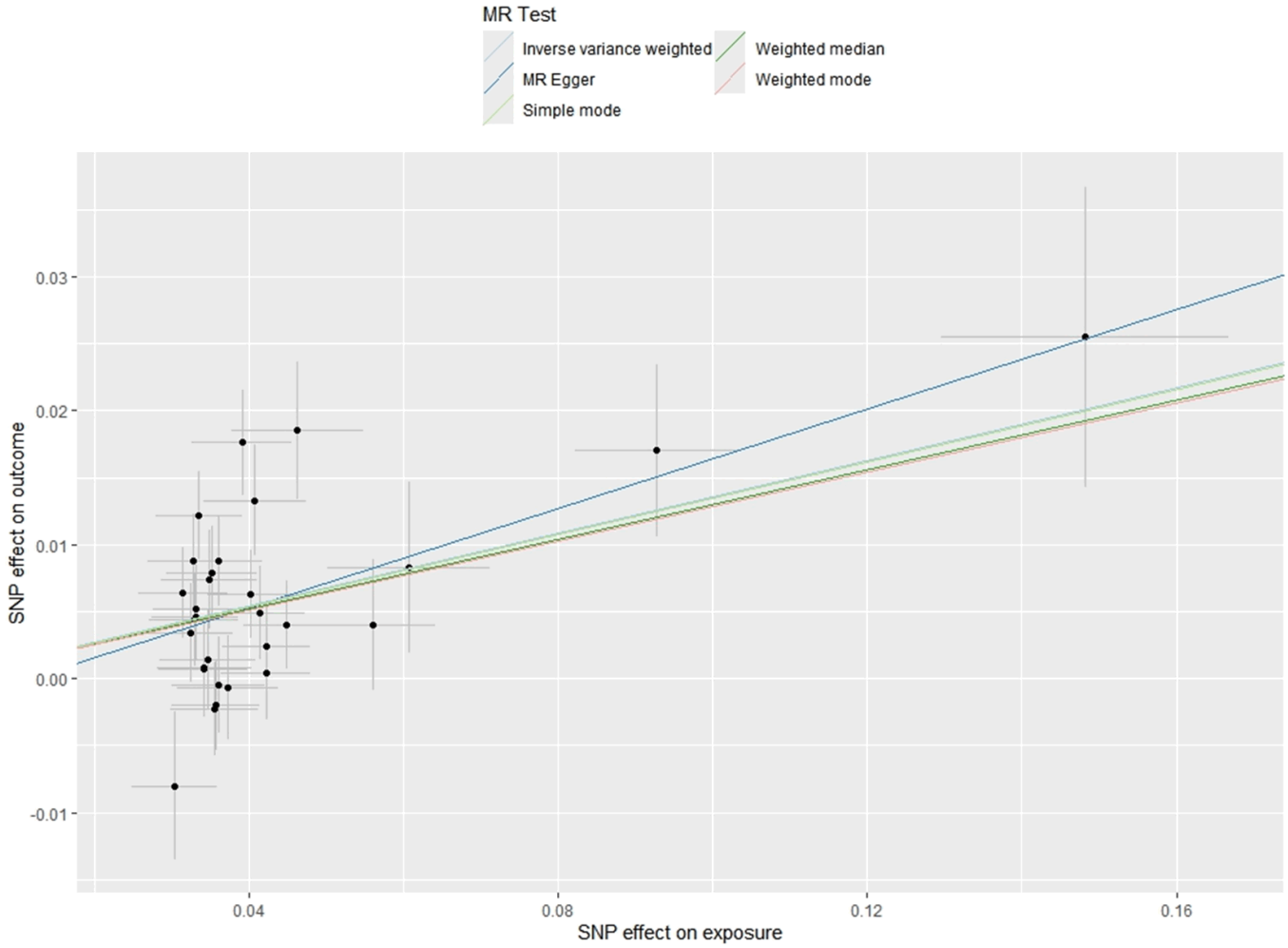

Figure 5. Scatter plots for the causal association between OA and frailty.

Among the shared genes discovered in this study, aside from some that have been previously identified as related to OA and frailty, the other genes have not been found to have a direct connection with these two traits. The relationship between the pathological processes they are involved in and traits studied warrants further discussion. The *GMPPB* gene encodes the enzyme guanosine diphosphate-mannose pyrophosphorylase B, which is crucial in the biosynthesis of GDP-mannose, an essential precursor for protein glycosylation [39]. Research has found that D-mannose can protect OA chondrocytes by reducing their sensitivity to ferroptosis, thereby slowing the progression of OA [40]. Its mutations result in decreased enzymatic activity, which correlates with the severity of muscle and neurological symptoms [41]. The *UBA7* gene, part of the *UBA* family, is involved in protein ubiquitination [42], which is crucial for maintaining protein homeostasis and function. Increasing research has found that various compounds targeting ubiquitination can regulate the development and progression of osteoarthritis [43]. Ubiquitination can also lead to a decreased stress response in the human body by regulating the stability and activity of inflammatory factors. We also found that *RAM6* and *ZCCHC4* were shared genes between OA and frailty, and their expressions were significantly associated with these traits, indicating underlying pathological mechanisms that warrant further exploration in the future. In summary, TWAS studies have identified pleiotropic genes that are significantly expressed in both frailty and osteoarthritis. These findings offer new insights into the development of targeted interventions for specific genetic variants or hereditary risk factors. Such interventions could include pharmacological treatments, behavioral therapies, or a combination of both, thereby laying the foundation for precision medicine in the management of these conditions.

FI is a comprehensive and multidimensional tool that measures an individual's level of frailty by considering health-related factors and functional abilities. Previous research has mostly focused on the relationship between FI and mood disorders. Elucidating its relationship with OA can help healthcare professionals identify and understand patient needs, and design targeted interventions to improve their quality of life and overall well-being.

Therefore, this study conducted MR analyses on the two traits and found that genetic variations in FI increase the

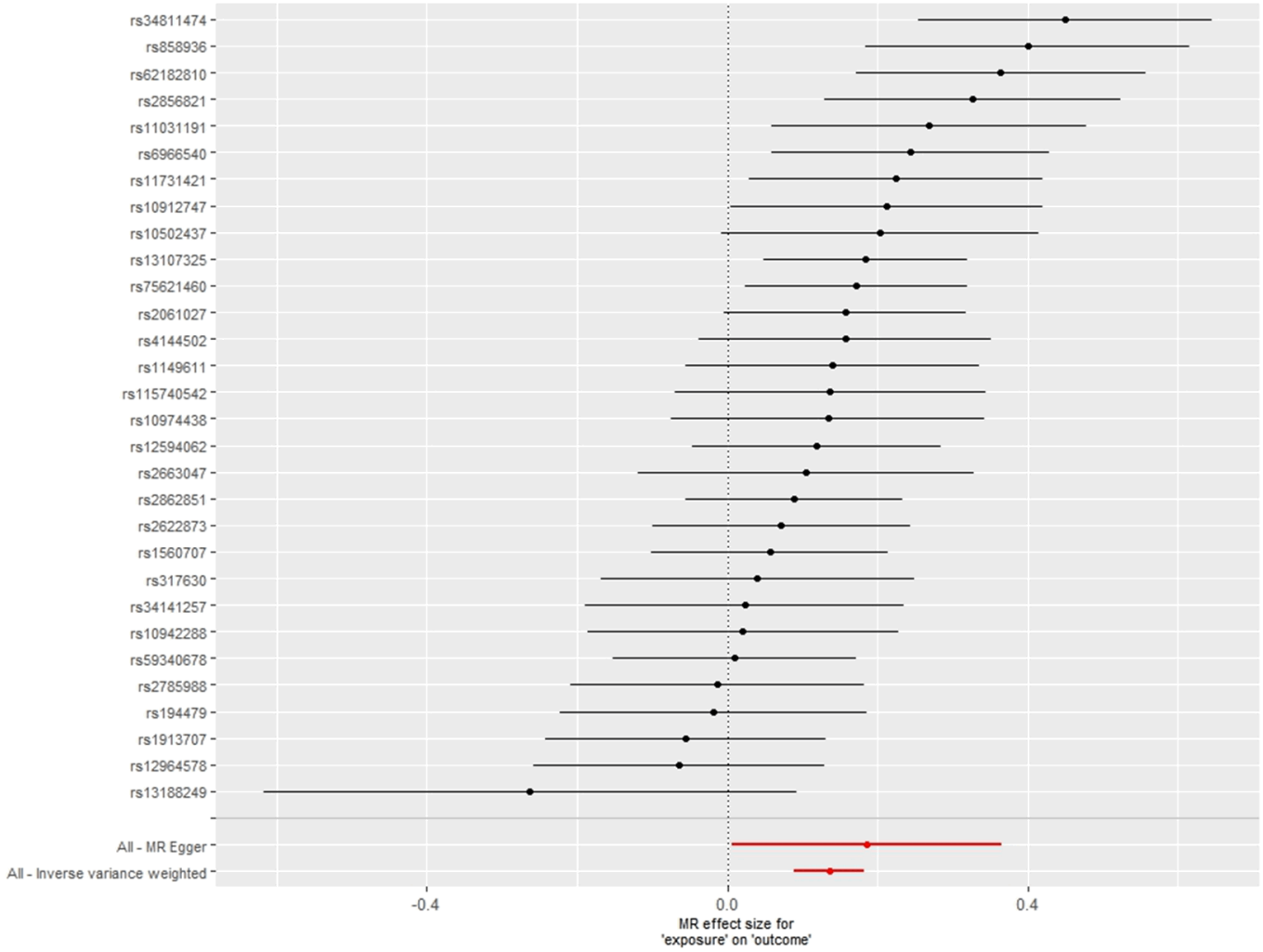

Figure 6. Leave-one-out for the causal association between OA and frailty.

risk of OA. This study's results are consistent with those of Huang et al. and show a more significant relationship between genetically mediated OA and frailty, possibly due to the larger GWAS sample size we included [44]. Additionally, Zhou et al. also used MR to find that hip and knee OA were risk factors for frailty [45]. Compared to their unidirectional study, this study used bidirectional MR, which not only provides a more comprehensive perspective to increases the credibility of the results but also considers the complex interactions between the two traits simultaneously. Additionally, we conducted a study on the shared genetic architecture of OA and frailty at the SNP and gene levels. The finding of these pleiotropic variants highlights the common etiology that underlies both OA and frailty, in which individuals with OA are inherently at a higher risk of supporting frailty the need for long-term, regular monitoring of abnormal conditions such as a decline in physical strength, fatigue, and weight loss in these individuals. Changes in modern lifestyles, including obesity, metabolic syndrome, alterations in dietary habits, and reduced physical activity, have been associated with the increased incidence of OA [46]. For instance, reducing sedentary behavior may help mitigate the risk of frailty. Engaging in moderate physical activity and maintaining healthy dietary habits can significantly reduce the risk of both OA and frailty [14]. In the context of modern living conditions, genetic factors may be insufficiently adapted to these rapidly changing environmental conditions. The interaction between environmental and genetic factors warrants further investigation as more data become available in the future.

The strength of this study lies in using the largest publicly available GWAS database, which is limited to the European population. Additionally, we analyzed the differences in OA imaging grades between frail and non-frail individuals. The genetic relationship between OA and frailty was explored systemically by employing multiple analytic frameworks. Finally, this study employed cross-trait analysis, which helps identify effective genetic loci that were previously overlooked in GWAS analyses. We acknowledge that this study has its limitations. The clinical data included in the study were limited. This is a preliminary exploration of the shared genetic architecture of OA

and frailty. In the future, more detailed classifications of OA, such as knee osteoarthritis and hip osteoarthritis, can be conducted. This would allow for more personalized detection schemes for populations with the same disease affecting different sites.

Conclusion

Compared with non-frail patients, the characteristics of X-ray and ^{18}F-FDG PET/CT in frail individuals were more severe. Additionally, our findings reveal shared genetic architecture and causal links between OA and frailty, which may underline the phenotypic relationship between OA and frailty. Early screening and intervention for frailty symptoms in OA populations can help reduce the risk and progression of frailty and related symptoms.

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Disclosure of conflict of interest

The authors declared that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

[1] Safiri S, Kolahi AA, Smith E, Hill C, Bettampadi D, Mansournia MA, Hoy D, Ashrafi-Asgarabad A, Sepidarkish M, Almasi-Hashiani A, Collins G, Kaufman J, Qorbani M, Moradi-Lakeh M, Woolf AD, Guillemin F, March L and Cross M. Global, regional and national burden of osteoarthritis 1990-2017: a systematic analysis of the global burden of disease study 2017. Ann Rheum Dis 2020; 79: 819-828.

[2] Clegg A, Young J, Iliffe S, Rikkert MO and Rockwood K. Frailty in elderly people. Lancet 2013; 381: 752-762.

[3] Moore AZ, Biggs ML, Matteini A, O'Connor A, McGuire S, Beamer BA, Fallin MD, Fried LP, Walston J, Chakravarti A and Arking DE. Polymorphisms in the mitochondrial DNA control region and frailty in older adults. PLoS One 2010; 5: e11069.

[4] Salaffi F, Farah S and Di Carlo M. Frailty syndrome in rheumatoid arthritis and symptomatic osteoarthritis: an emerging concept in rheumatology. Acta Biomed 2020; 91: 274-296.

[5] Salaffi F, Di Carlo M, Carotti M, Farah S and Giovagnoni A. Frailty prevalence according to the Survey of Health, Ageing and Retirement in Europe-Frailty Instrument (SHARE-FI) definition, and its variables associated, in patients with symptomatic knee osteoarthritis: findings from a cross-sectional study. Aging Clin Exp Res 2021; 33: 1519-1527.

[6] Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, Bridgett L, Williams S, Guillemin F, Hill CL, Laslett LL, Jones G, Cicuttini F, Osborne R, Vos T, Buchbinder R, Woolf A and March L. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014; 73: 1323-1330.

[7] D'Agnelli S, Amodeo G, Franchi S, Verduci B, Baciarello M, Panerai AE, Bignami EG and Sacerdote P. Frailty and pain, human studies and animal models. Ageing Res Rev 2022; 73: 101515.

[8] O'Brien MS and McDougall JJ. Age and frailty as risk factors for the development of osteoarthritis. Mech Ageing Dev 2019; 180: 21-28.

[9] Joo SH, Song JW, Shin K, Kim MJ, Lee J and Song YW. Knee osteoarthritis with a high grade of Kellgren-Lawrence score is associated with a worse frailty status, KNHANES 2010-2013. Sci Rep 2023; 13: 19714.

[10] Cai G, Zhang Y, Wang Y, Li X, Xu S, Shuai Z, Pan F and Peng X. Frailty predicts knee pain trajectory over 9 years: results from the osteoarthritis initiative. Pain Med 2023; 24: 1364-1371.

[11] Cook MJ, Verstappen SMM, Lunt M and O'Neill TW. 514 frailty in osteoarthritis and the influence of co-morbidity. Age Ageing 2021; 50: ii5-ii7.

[12] Vennu V, Alsaad SM, Alenazi AM and Bindawas SM. Association between musculoskeletal pain and frailty over time in older adults. J Geriatr Phys Ther 2024; [Epub ahead of print].

[13] Albala C, Marquez C, Angel B, Saguez R and Lera L. Frailty and osteoarthritis in older Chileans. Innov Aging 2022; 6: 561-562.

[14] Song J, Lindquist LA, Chang RW, Semanik PA, Ehrlich-Jones LS, Lee J, Sohn MW and Dunlop DD. Sedentary behavior as a risk factor for physical frailty independent of moderate activity: results from the osteoarthritis initiative. Am J Public Health 2015; 105: 1439-1445.

[15] Chen Q, Gan D, Zhang Y, Yan R, Li B, Tang W, Han S and Gao Y. Causal relationship between neuroticism and frailty: a bidirectional Mendelian randomization study. J Affect Disord 2024; 360: 71-78.

[16] Wang Z, Dou Y, Chen L, Feng W, Zou Y, Xiao J, Wang J and Zou Z. Mendelian randomization identifies causal effects of major depressive disorder on accelerated aging. J Affect Disord 2024; 358: 422-431.

[17] Richette P and Latourte A. Osteoarthritis: value of imaging and biomarkers. Rev Prat 2019; 69: 507-509.

[18] Erol Fenercioğlu Ö, Beyhan E, Ergül N, Arslan E and Çermik TF. 18F-FDG PET/CT and 68Ga-FAPI-4 PET/CT findings of bilateral knee osteoarthritis in a patient with uveal malignant melanoma. Clin Nucl Med 2022; 47: e144-e146.

[19] Wu J, Chen B, Mao Y, Li S, Zhao W, Meng D, Hu S, Wang J, Yu P, Zhang C and Wu J; Geriatrics Branch, Chinese Medical Association, and the expert group of the Chinese Expert Consensus on Prevention and Control Interventions for Older Adults with Physical Functional Impairment. Chinese expert consensus on prevention and control interventions for older adults with physical functional impairment (2022). Aging Med (Milton) 2023; 6: 25-34.

[20] Marijnissen AC, Vincken KL, Vos PA, Saris DB, Viergever MA, Bijlsma JW, Bartels LW and Lafeber FP. Knee Images

Digital Analysis (KIDA): a novel method to quantify individual radiographic features of knee osteoarthritis in detail. Osteoarthritis Cartilage 2008; 16: 234-243.
[21] Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S and Yang J; Schizophrenia Working Group of the Psychiatric Genomics Consortium; Patterson N, Daly MJ, Price AL and Neale BM. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet 2015; 47: 291-295.
[22] Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR and Loh PR; ReproGen Consortium; Psychiatric Genomics Consortium; Genetic Consortium for Anorexia Nervosa of the Wellcome Trust Case Control Consortium 3; Duncan L, Perry JR, Patterson N, Robinson EB, Daly MJ, Price AL and Neale BM. An atlas of genetic correlations across human diseases and traits. Nat Genet 2015; 47: 1236-1241.
[23] Wallace C. Eliciting priors and relaxing the single causal variant assumption in colocalisation analyses. PLoS Genet 2020; 16: e1008720.
[24] Watanabe K, Taskesen E, van Bochoven A and Posthuma D. Functional mapping and annotation of genetic associations with FUMA. Nat Commun 2017; 8: 1826.
[25] de Leeuw CA, Mooij JM, Heskes T and Posthuma D. MAGMA: generalized gene-set analysis of GWAS data. PLoS Comput Biol 2015; 11: e1004219.
[26] Gusev A, Ko A, Shi H, Bhatia G, Chung W, Penninx BW, Jansen R, de Geus EJ, Boomsma DI, Wright FA, Sullivan PF, Nikkola E, Alvarez M, Civelek M, Lusis AJ, Lehtimäki T, Raitoharju E, Kähönen M, Seppälä I, Raitakari OT, Kuusisto J, Laakso M, Price AL, Pajukanta P and Pasaniuc B. Integrative approaches for large-scale transcriptome-wide association studies. Nat Genet 2016; 48: 245-252.
[27] Sekula P, Del Greco MF, Pattaro C and Köttgen A. Mendelian randomization as an approach to assess causality using observational data. J Am Soc Nephrol 2016; 27: 3253-3265.
[28] Mullin BH, Zhu K, Brown SJ, Mullin S, Dudbridge F, Pavlos NJ, Richards JB, Grundberg E, Bell JT, Zeggini E, Walsh JP, Xu J and Wilson SG. Leveraging osteoclast genetic regulatory data to identify genes with a role in osteoarthritis. Genetics 2023; 225: iyad150.
[29] Song Z, Li W, Han Y, Xu Y and Wang Y. Investigating the shared genetic architecture between frailty and insomnia. Front Aging Neurosci 2024; 16: 1358996.
[30] Castle A and Castle D. Ubiquitously expressed secretory carrier membrane proteins (SCAMPs) 1-4 mark different pathways and exhibit limited constitutive trafficking to and from the cell surface. J Cell Sci 2005; 118: 3769-3780.
[31] Cao THM, Le APH, Tran TT, Huynh VK, Pham BH, Le TM, Nguyen QL, Tran TC, Tong TM, Than THN, Nguyen TTT and Ha HTT. Plasma cell-free RNA profiling of Vietnamese Alzheimer's patients reveals a linkage with chronic inflammation and apoptosis: a pilot study. Front Mol Neurosci 2023; 16: 1308610.
[32] Ye H, Cai T, Shen Y, Zhao L, Zhang H, Yang J, Li F, Chen J and Shui X. MST1 knockdown inhibits osteoarthritis progression through Parkin-mediated mitophagy and Nrf2/NF-κB signalling pathway. J Cell Mol Med 2024; 28: e18476.
[33] Hao X, Zhao J, Jia L, He T, Wang H, Fan J, Yang Y, Su F, Lu Q, Zheng C, Yang L and Jie Q. XMU-MP-1 attenuates osteoarthritis via inhibiting cartilage degradation and chondrocyte apoptosis. Front Bioeng Biotechnol 2022; 10: 998077.
[34] Li W, Deng Y, Feng B and Mak KK. Mst1/2 kinases modulate glucose uptake for osteoblast differentiation and bone formation. J Bone Miner Res 2018; 33: 1183-1195.
[35] Ferrucci L and Zampino M. A mitochondrial root to accelerated ageing and frailty. Nat Rev Endocrinol 2020; 16: 133-134.
[36] Rawat SJ, Creasy CL, Peterson JR and Chernoff J. The tumor suppressor Mst1 promotes changes in the cellular redox state by phosphorylation and inactivation of peroxiredoxin-1 protein. J Biol Chem 2013; 288: 8762-8771.
[37] Xiao L, Chen D, Hu P, Wu J, Liu W, Zhao Y, Cao M, Fang Y, Bi W, Zheng Z, Ren J, Ji G, Wang Y and Yuan Z. The c-Abl-MST1 signaling pathway mediates oxidative stress-induced neuronal cell death. J Neurosci 2011; 31: 9611-9619.
[38] Morrison AC, Wilson CB, Ray M and Correll PH. Macrophage-stimulating protein, the ligand for the stem cell-derived tyrosine kinase/RON receptor tyrosine kinase, inhibits IL-12 production by primary peritoneal macrophages stimulated with IFN-gamma and lipopolysaccharide. J Immunol 2004; 172: 1825-1832.
[39] Zheng L, Liu Z, Wang Y, Yang F, Wang J, Huang W, Qin J, Tian M, Cai X, Liu X, Mo X, Gao N and Jia D. Cryo-EM structures of human GMPPA-GMPPB complex reveal how cells maintain GDP-mannose homeostasis. Nat Struct Mol Biol 2021; 28: 1-12.
[40] Zhou X, Zheng Y, Sun W, Zhang Z, Liu J, Yang W, Yuan W, Yi Y, Wang J and Liu J. D-mannose alleviates osteoarthritis progression by inhibiting chondrocyte ferroptosis in a HIF-2α-dependent manner. Cell Prolif 2021; 54: e13134.
[41] Franzka P, Henze H, Jung MJ, Schüler SC, Mittag S, Biskup K, Liebmann L, Kentache T, Morales J, Martínez B, Katona I, Herrmann T, Huebner AK, Hennings JC, Groth S, Gresing L, Horstkorte R, Marquardt T, Weis J, Kaether C, Mutchinick OM, Ori A, Huber O, Blanchard V, von Maltzahn J and Hübner CA. GMPPA defects cause a neuromuscular disorder with α-dystroglycan hyperglycosylation. J Clin Invest 2021; 131: e139076.
[42] Guo Y, Liu Q, Zheng Z, Qing M, Yao T, Wang B, Zhou M, Wang D, Ke Q, Ma J, Shan Z and Chen W. Genetic association of inflammatory marker GlycA with lung function and respiratory diseases. Nat Commun 2024; 15: 3751.
[43] Zheng C, Chen J, Wu Y, Wang X, Lin Y, Shu L, Liu W and Wang P. Elucidating the role of ubiquitination and deubiquitination in osteoarthritis progression. Front Immunol 2023; 14: 1217466.
[44] Huang G, Qian D, Liu Y, Qu G, Qian Y and Pei B. The association between frailty and osteoarthritis based on the NHANES and Mendelian randomization study. Arch Med Sci 2023; 19: 1545-1550.
[45] Zhou J, Li Y, Lin Y, Wang F, Tian J, Wang Y, Bi Q, Wang C and Zhao T. The genetic causal association between hip or knee osteoarthritis and frailty: a two-sample Mendelian randomization analysis. Arch Med Sci 2024; 20: 938-946.
[46] Berenbaum F, Wallace IJ, Lieberman DE and Felson DT. Modern-day environmental factors in the pathogenesis of osteoarthritis. Nat Rev Rheumatol 2018; 14: 674-681.