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Genome-Wide Crossover Analysis Identification of Shared Genetic Effect Site between Frailty and Multiple Psychiatric Disorders[1]

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Abstract

Frailty, a geriatric syndrome marked by reduced physiological reserves, shares significant biological and pathological mechanisms with psychiatric disorders such as depression, anxiety, and sleep disorders, yet their shared genetic underpinnings remain poorly understood. This study aimed to elucidate the genetic correlations and pleiotropic mechanisms linking frailty with these psychiatric conditions by leveraging genome-wide association study (GWAS) summary statistics and advanced cross-trait pleiotropy analyses. A total of 748 pleiotropic single-nucleotide polymorphisms

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(SNPs) were identified, with 36 loci confirmed as dominant risk factors and 20 validated through causal co-localization analysis. Gene-level analyses pinpointed key pleiotropic genes (e.g., TTC12, TMOD2, and AMT), and pathway enrichment analyses revealed significant involvement of synaptic plasticity, arginine metabolism, and complement24 dependent cytotoxicity regulation. Tissue-specific enrichment highlighted the hypothalamus, frontal cortex, and pituitary as critical sites, while immune co26 localization analyses implicated B cells, dendritic cells, and myeloid subsets in disease mediation. These findings underscore the shared genetic and immune regulatory mechanisms underlying frailty and psychiatric disorders, providing novel insights into their interconnected pathophysiology and identifying potential therapeutic targets. This study not only bridges critical gaps in the understanding of these conditions but also offers a foundation for precision medicine strategies to improve clinical outcomes in aging populations.

Keywords

Genetic Overlap, Frailty, Psychiatric disorders.

Introduction

Frailty, a prevalent geriatric syndrome, is characterized by diminished physiological reserve and reduced resilience to external stress, resulting in a comprehensive decline in physical fitness, mobility, and overall health. Its pathological basis lies in the disruption of multi-system homeostasis, including dysfunction of the nervous, endocrine-metabolic, and immune systems[1]. Psychiatric disorders, characterized by disturbances in cognition, emotional regulation, and behavior, often lead to significant personal distress and impaired daily functioning[2]. Notably, both frailty and psychiatric disorders are strongly associated with chronic systemic low-grade inflammation, a phenomenon termed *"inflammaging"* in elderly populations[3–6]. Elevated levels of C reactive protein (CRP) and pro-inflammatory cytokines such as IL-6 and TNF-α not only contribute to the onset of psychiatric disorders but also accelerate frailty progression[4,7]. Sustained activation of these inflammatory cytokines can induce neuroinflammation, impair central nervous system function, and exacerbate psychiatric symptoms. Additionally, overactivation of the hypothalamic-pituitary-adrenal (HPA) axis leads to elevated cortisol levels, which inhibit neurogenesis and promote symptoms of anxiety and depression[8]. Meanwhile, dysfunction of neurotransmitter systems, exacerbated by neuronal impairment, further accelerates the progression of frailty. Collectively, these findings underscore the existence of shared biological mechanisms between frailty and psychiatric disorders, highlighting their interconnected pathophysiological processes.

Epidemiological studies strongly support the association between frailty and various psychiatric disorders. For instance, compared to the healthy population, frail individuals face approximately 1.5 times higher risk of sleep disorders, a threefold increase in the risk of major depressive disorder, and a 2.5-fold increase in the incidence of anxiety. Among hospitalized elderly patients with psychiatric disorders, frailty prevalence reaches as high as 52.5% to 59.2%[9]. Assessments using the Pittsburgh

Sleep Index have revealed significantly higher rates of sleep disorders in the pre-frailty and frailty groups (37% and 37.6%, respectively) compared to the control group[10]. Multivariate logistic regression analysis further confirms that poor sleep quality is an independent risk factor for frailty[11]. While prior studies have identified associations between frailty and individual psychiatric disorders, they primarily focus on observational evidence and lack systematic investigation into the pleiotropic mechanisms underlying multiple psychiatric disorders and frailty. For example, research by Atkins et al. suggests that the shared mechanisms between depression and frailty may involve genetic functions within the prefrontal cortex and hippocampus[12]. However, the genetic basis of frailty remains incompletely understood, with heritability estimates ranging between 30% and 45%[13]. Candidate gene association studies have implicated genes such as IL-18 in frailty-related inflammatory pathways[14]. Given these significant knowledge gaps, there is an urgent need for comprehensive exploration of shared genetic risk loci to better understand the common biological mechanisms linking frailty and psychiatric disorders.

In recent years, methods such as high-resolution likelihood (HDL) and linkage disequilibrium score regression (LDSC) based on aggregated GWAS data have been developed to uncover genetic correlations between diseases[15,16]. However, it remains unclear whether these correlations arise from effects at specific loci or across the entire genome. Cross-trait analyses have proven effective in identifying shared loci between diseases, which can serve as potential therapeutic targets and offer novel insights into disease prevention and treatment[17–19]. Utilizing the newly developed pleiotropy analysis method (PLACO) under the composite null hypothesis[20], this study aims to identify pleiotropic genetic loci at the SNP level and provide a deeper understanding of the shared genetic mechanisms underlying complex diseases. Our research flowchart is shown in Fig. 1.

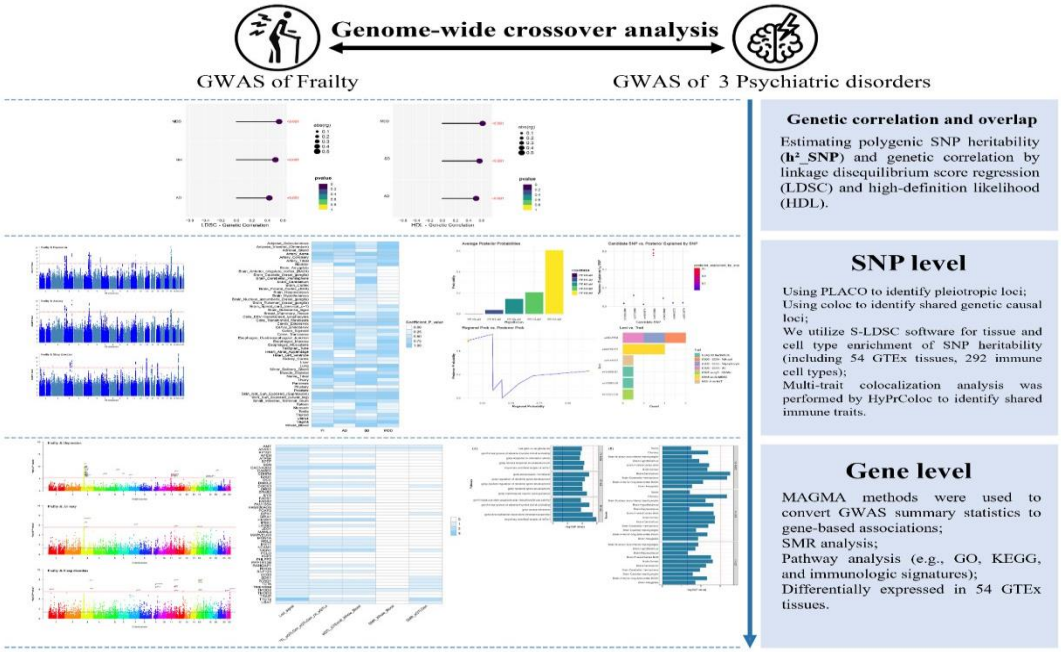

Fig. 1 Study workflow

Methods

GWAS summary data source

The GWAS summary statistics for the three psychiatric disorders analyzed in this study were obtained from publicly available large-scale GWAS databases[21]. Frailty GWAS data (GWAS ID: ebi-a-GCST90020053) were derived from two meta-analyses: the UK Biobank cohort of European ancestry (n = 164,610) and the Swedish TwinGene study (n = 10,616)[12]. A standardized quality control protocol was applied across all datasets, assessing the association between frailty and SNP genotypes using logistic regression analysis. Risk estimates were subsequently combined through meta-analysis using the ixed-effects inverse variance weighting (IVW) method[22]. Data for all three mental disorders were obtained from the FinnGen R11 database (GWAS ID for depressive disorder: finngen_R11_F5_DEPRESSIO, GWAS ID for anxiety disorder: finngen_R11_F5_ALLANXIOUS, GWAS ID for sleep disorders: finngen_R11_SLEEP)[21]. The sources and details of these datasets are summarized in 114 Additional file 2: Table S1.

Quality control

To ensure data accuracy and reliability, rigorous quality control measures were applied. First, SNPs within the major histocompatibility complex (MHC) region, spanning the 25 Mb to 35 Mb interval on chromosome 6, were excluded from the analysis[23]. Due to its highly complex gene structure and extensive linkage disequilibrium, this region is prone to false-positive results and is typically excluded in GWAS studies. Second, to minimize the impact of rare variations, a minor allele frequency (MAF) threshold was set at >0.01, retaining only SNPs with a minor allele frequency greater than 1%. This filtering step ensures a focus on common variants, thereby improving statistical power and reducing the likelihood of false positives. Additionally, checks for sample and marker quality were performed. For samples, a call rate threshold of >95% was applied, while for markers, a stricter call rate threshold of >99% was enforced. Samples and markers failing to meet these criteria were excluded to maintain data integrity and ensure the robustness of the analysis.

Genomic wide genetic association analysis

To investigate the shared genetic framework between psychiatric disorders and frailty, linkage LDSC was utilized[15]. The linkage disequilibrium (LD) scores for this analysis were derived from common SNP genotypes of European ancestry samples provided by the 1000 Genomes Project[24]. The standard error (SE) was estimated using the leave one-out method, which was then applied to adjust for attenuation bias. Furthermore, the LDSC intercept was employed to assess potential population overlap among the datasets[15]. Notably, our analysis confirmed no population overlap between the datasets for psychiatric disorders and frailty, thereby enhancing the reliability of the results.To further validate the findings from LDSC, we utilized HDL, a likelihood-based analytical tool. HDL leverages GWAS summary statistics more effectively than LDSC, reducing the variance in genetic association estimates by approximately 60%. This results in significantly improved accuracy and robustness[16]. By cross-

validating the LDSC results with HDL, we ensured the reliability and robustness of the genetic overlap analysis.

Recognition of pleiotropy loci

In this study, we employed the PLACO method to systematically identify genetic associations between frailty and three types of psychiatric disorders at the SNP level. PLACO is a statistical approach specifically designed to detect gene pleiotropy, enabling the identification of shared genetic variants across multiple phenotypes. Using this method, we effectively identified SNPs that demonstrate significant associations with multiple diseases[25].

SNPs reaching genome-wide significance ($P < 5 \times 10^{-8}$) were classified as pleiotropic variants, indicating their strong genetic associations with multiple phenotypes and their potential role in the pathogenesis of these conditions. Identifying such pleiotropic variants is crucial for uncovering the shared genetic basis between psychiatric disorders and frailty. To further validate the biological significance of these pleiotropic SNPs, we utilized the Functional Mapping and Annotation (FUMA) tool, which enables mapping of risk variants to specific genomic regions (i.e., risk loci), providing deeper insights into their potential functions. Additionally, Bayesian co-localization analysis was performed to identify loci shared by frailty and psychiatric disorders[26].

Tissue-specific enrichment analysis

To investigate the genetic associations between frailty and psychiatric disorders across different tissues and organs, this study analyzed the enrichment of SNP heritability in specific cell and tissue types. Stratified-LDSC (S-LDSC) was employed to evaluate GWAS summary statistics for various tissues and organs, identifying the genetic enrichment significance of specific traits. Expression data for 54 human tissues were obtained from the GTEx database and analyzed using the S-LDSC method to assess SNP heritability enrichment levels for each tissue and cell type[27]. These steps ensured both the accuracy and robustness of the analysis. Ultimately, this study aims to uncover potential shared genetic mechanisms underlying frailty and psychiatric disorders.

Gene level pleiotropy analysis

To explore the mechanisms underlying the identified loci, nearby genes were mapped based on the dominant SNPs within each locus. The Generalized Gene Set Analysis (MAGMA) method was applied to evaluate the multi-trait effects of GWAS data and determine the biological roles of these pleiotropic gene loci. Specifically, MAGMA gene analysis identified pleiotropic genes by incorporating LD between SNPs and detecting multi-trait effects ($P < 0.05/18{,}345 = 2.73 \times 10^{-6}$)[28]. Additionally, MAGMA gene cluster analysis was performed to investigate the biological roles of dominant SNPs[28]. Gene sets from the Molecular Signatures Database (MSigDB), including curated gene sets (c2.all) and Gene Ontology categories (c5.bp, c5.cc, and c5.mf), were analyzed. To reduce the likelihood of false positives, Bonferroni correction was applied to all gene sets ($P < 0.05/10{,}678 = 4.68 \times 10^{-6}$)[29].

Pathway enrichment analysis was conducted using the Metascape web tool (metascape.org) to identify the functions of the mapped genes based on the MSigDB database[30]. Additionally, genome-wide tissue-specific enrichment analysis was performed on pleiotropic results obtained from PLACO,

utilizing expression data from 54 GTEx tissues. For this analysis, the average expression levels of all identified pleiotropic genes were log2-transformed across the 54 GTEx tissues. Tissue-specific tests were then carried out using differential expression genes (DEGs) in each tissue, with upregulated and downregulated DEGs pre-classified based on the direction of the t-statistic.

Exploration of drug targets in European populations

The Mendelian randomization (SMR) method, utilizing summary-level data, combines GWAS summary statistics with expression quantitative trait loci (eQTL) data to uncover gene expression levels associated with complex traits via pleiotropy[31]. eQTL represents genetic variants that impact gene expression levels, helping to explain individual differences in gene expression. By examining the relationship between specific SNPs and gene expression levels, eQTL studies can identify genetic variations that influence gene expression.

The SMR framework integrates eQTL data with GWAS data to investigate the potential mechanisms through which SNPs affect complex traits, including diseases. Using the SMR and HEterogeneity in Dependent Instrument (HEIDI) methods, pleiotropic associations between gene expression and complex traits are evaluated. The primary objective of SMR analysis is to assess whether the impact of an SNP on a phenotype is mediated by alterations in gene expression. If an SNP is linked to both gene expression and complex traits, this suggests pleiotropy, indicating that the gene may play a pivotal role in the genetic foundation of these traits.

The HEIDI test further investigates whether the observed association is due to co-localization, examining whether the effects of SNPs on gene expression and their effects on complex traits originate from the same causal variant[32]. If the HEIDI test confirms co-localization, the association is attributed to shared causal variants between loci, rather than a single pleiotropic effect. This distinction improves our understanding of the genetic mechanisms underlying these complex traits.

The SMR method thus serves a dual purpose: identifying genes shared between psychiatric disorders and frailty and uncovering regulatory mechanisms linking genetic variation to phenotype. These insights provide valuable clues for the discovery of novel therapeutic targets.

Co-immunoprecipitation analysis

We developed a novel co-immunoprecipitation method by integrating extensive immune GWAS data, publicly available from the GWAS catalog, covering 731 immune cell types[33]. Building on our previous hypothesis prioritization for multi-trait colocalization (HyPrColoc) method, this method significantly enhances the precision of identifying the roles of immune traits in complex diseases. Moreover, it effectively identifies and evaluates the plausibility of potential immune mediation models. This improved approach offers a fresh perspective for advancing our understanding of the immune system's regulatory mechanisms in the context of psychiatric disorders and frailty. Detailed information on the GWAS summary datasets for immune cells was added to Additional file 1: Supplementary Methods.

Software

The primary statistical analyses were conducted using R (version 3.5.3). LDSC and S230 LDSC analyses were executed with the "LDSC" software (v1.0.1)[34], while "PLACO" package[20] was used for PLACO analysis. Bayesian colocalization was carried out with the "coloc" package (v5.2.1)[32], and HyPrColoc analysis utilized the "hyprcoloc" package (v1.0)[35]. Functional analysis was performed via the FUMA web tool[36], and MAGMA gene and gene-set analyses were conducted using MAGMA software[28].

Result

The shared genetic structure between psychiatric disorders and frailty

This study evaluated the genetic correlations between major depressive disorder (MDD), anxiety disorder (AX), sleep disorder (SD), and frailty using both LDSC and HDL methods. The results from these analyses were highly consistent, demonstrating a significant genetic correlation ($P < 0.01$) between frailty and the three psychiatric disorders (Table 1 and Additional file 2: Table S2).

Table 1 Genetic correlation between psychiatric disorders and frailty

Trait pairs	LDSC		HDL	
	r_g(SE)	P	r_g(SE)	P
MDD	0.5506(0.0264)	1.9636e-96	0.6158(0.0311)	1.99e-87
AX	0.4236(0.0296)	1.56e-46	0.5162(0.0332)	1.52e-54
SD	0.5019(0.0289)	8.9428e-68	0.5692(0.0291)	2.79e-85

These findings indicate the existence of a significant shared genetic mechanism underlying frailty and the three psychiatric disorders. Furthermore, the HDL method, with its lower estimation variance, reinforced the robustness of the genetic correlation analyses, confirming that all three traits share a common genetic basis to some degree. This provides compelling evidence of genetic overlap between frailty and psychiatric disorders, highlighting their shared genetic background as a potential focal point for developing prevention and treatment strategies.

Identification and confirmation of polymorphic risk SNP loci for multiple psychiatric disorders and frailty

Building on the genetic correlations revealed by the LDSC and HDL methods, the PLACO method was employed to identify and validate pleiotropic risk SNP loci. A total of 1,055 novel SNP loci associated with frailty and psychiatric disorders were identified ($P < 5 \times 10^{-8}$), of which 748 loci passed Bonferroni correction. Specifically, among the 527 loci associated with frailty and depression, 395 loci passed correction ($P < 0.05/4,051,101$); among the 96 loci associated with frailty and anxiety, 57 loci passed correction; and among the 432 loci associated with frailty and sleep disorders, 296 loci passed correction ($P < 0.05/4,051,051$) (Additional file 2: table S3). Across the three analyses, four loci

(*rs536445, rs12635614, rs3752769,* and *rs3752768*) reached genome-wide significance, exhibiting pleiotropic associations with all three psychiatric disorders and frailty (Table 2).

Table 2 Multiple trait shared SNPs

SNP	FI-MDD		FI-AX		FI-SD	
	T	p	T	p	T	p
rs536445	26.29074	4.96E-11	25.13737	8.59E-11	20.52155	7.57E-09
rs12635614	25.1242	1.38E-10	22.77734	7.07E-10	23.24552	6.91E-10
rs3752769	24.4181	2.55E-10	22.76959	7.12E-10	21.63858	2.83E-09
rs3752768	25.05183	1.47E-10	22.46289	9.36E-10	22.67207	1.14E-09

Further analysis using the FUMA tool, based on PLACO results, confirmed 36 dominant risk SNP loci significantly associated with frailty and psychiatric disorders (Additional file 2: Table S4). Among these, 16 loci were linked to frailty and depression (Additional file 1: Fig. S3), 7 to frailty and anxiety (Additional file 1: Fig. S4), and 12 to frailty and sleep disorders (Additional file 1: Fig. S5).

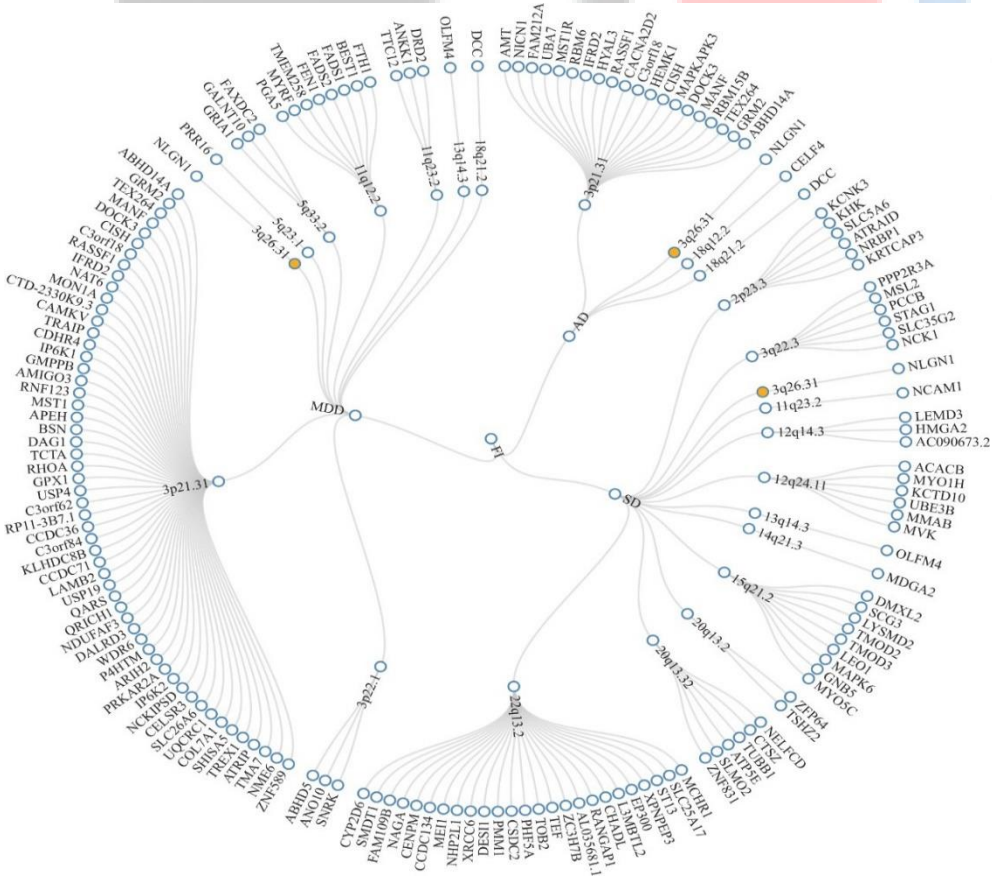

Fig. 2 The circular diagram presents pleiotropic loci and genes identified by PLACO among three trait pairs. Note: Multi-trait shared loci highlighted in orange. FI frailty, MDD depression, AD anxiety, SD sleep disorders

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Additionally, co-localization analysis identified 20 potential pleiotropic loci with PP.H4 values (posterior probability for shared causal variants) greater than 0.7 (Additional file 2: Table S5). Notably, the genomic region 3q26.31 exhibited significant co-localization for frailty and all three psychiatric disorders, further emphasizing its critical role in shared genetic mechanisms (Fig. 1 and Additional file 2 Table S6).

Organ association results

This study employed the S-LDSC method to assess SNP heritability enrichment for psychiatric disorders and frailty across various cell and tissue types. Data from 54 human tissues provided by the GTEx database were analyzed to identify significant SNP heritability enrichment in specific tissues. This significance was evaluated using regression coefficient Z-scores and corresponding P-values, adjusted for the baseline model and all relevant gene sets.

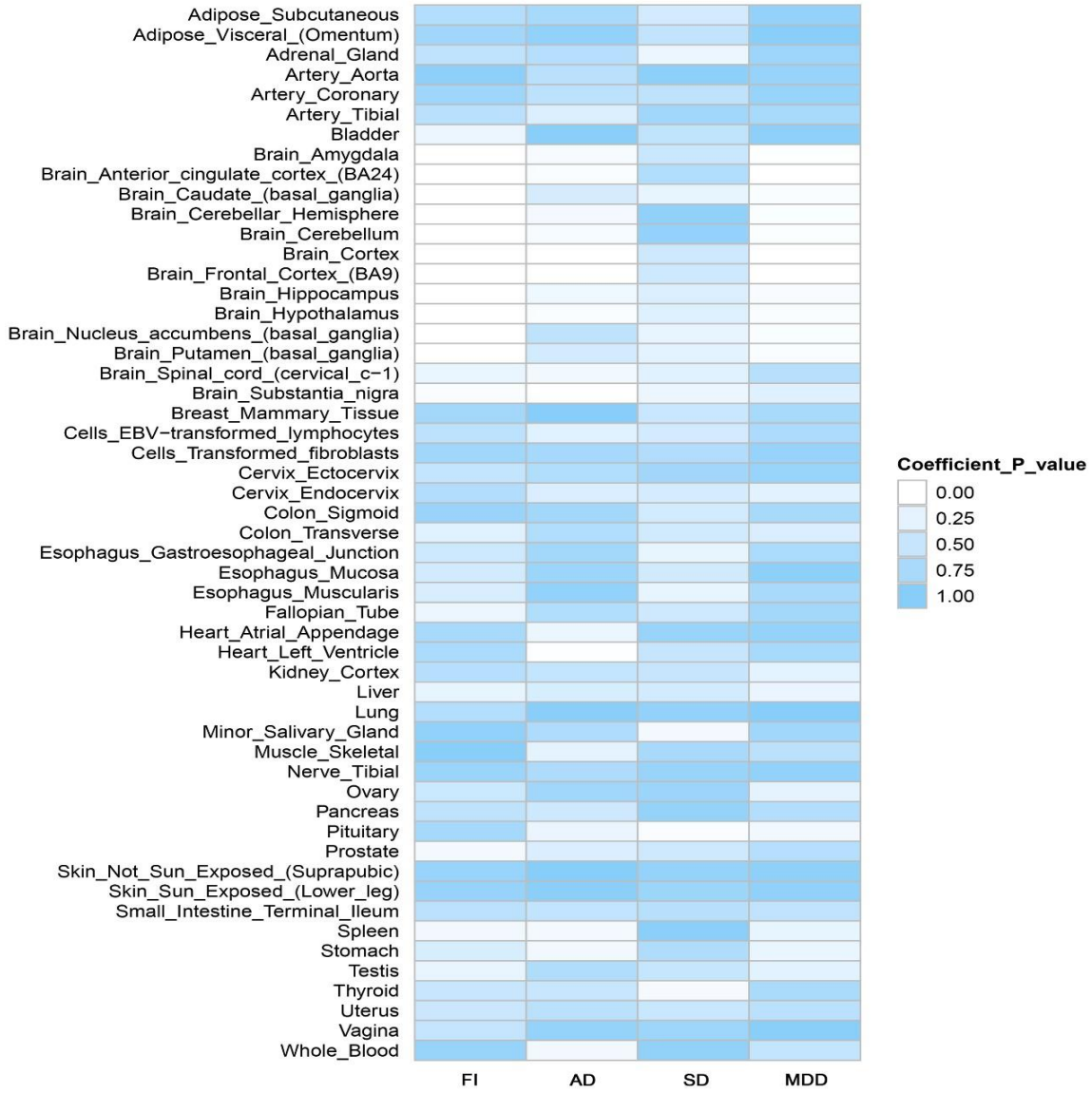

Fig. 3 Heat maps of tissue and organ features common between mental disorders and debilitating disorders identified by S-LDSC. Abbreviations: FI frailty, MDD depression, AD anxiety, SD sleep disorders

The tissue-specific analysis identified significant genetic enrichment of frailty GWAS data in multiple brain regions, including the frontal cortex (BA9) , brain cortex, anterior cingulate cortex (BA24) , amygdala, hippocampus, hypothalamus, cerebellum, cerebellar hemisphere, caudate, putamen, and nucleus accumbens. For depression, enrichment was primarily found in the anterior cingulate cortex (BA24), brain cortex, frontal cortex (BA9), amygdala, cerebellar hemisphere, and cerebellum. Anxiety showed genetic enrichment predominantly in the substantia nigra, frontal cortex (BA9) , brain cortex, and heart left ventricle. In contrast, sleep disorders did not exhibit notable genetic enrichment across the 54 tissues analyzed; however, the pituitary and thyroid displayed the highest and second-highest levels of enrichment, respectively (Additional file 2 Table S7).

A comparison of tissues significantly enriched for different traits revealed that the frontal cortex (BA9) and brain cortex were commonly enriched in depression, anxiety, and frailty (Fig. 2). Notably, the tissues with significant enrichment were predominantly concentrated in the nervous and endocrine systems, underscoring their pivotal roles in the shared pathological mechanisms underlying psychiatric disorders and frailty.

MAGMA gene hierarchical analysis

Using the FUMA tool, this study conducted MAGMA gene analysis for frailty and three psychiatric disorders ($P < 0.05/18{,}167$, FDR < 0.05). The analysis identified 36enriched genes significantly associated with both frailty and depression, 6 enriched genes significantly associated with both frailty and anxiety, and 18 enriched genes significantly associated with both frailty and sleep disorders (Fig. 3 and Additional file 2 Table S8). Further pathway enrichment analysis revealed that 110 signaling pathways were significantly enriched by genes related to all four conditions. Among these, the top five significant pathways demonstrated that shared genes are involved in multiple key biological pathways and processes, including the development and regulation of the postsynaptic membrane and dendritic spines, axonal guidance, DNA groove adenine-thymidine-rich binding regions, nitrosative stress response, cellular response to ammonium ions, regulation of *let-7a1* targeting cancer fetal markers, NAD^+-dependent ADP-ribosyl transferase activity, adhesion bands, and DNA replication358 dependent chromatin assembly (Fig. 4A and Additional file 2 Table S9).

Tissue-specific analysis of the gene sets showed that the enriched genes exhibited specific expression patterns in various tissues and organs, including the cerebral cortex, cerebellum, cerebellar hemispheres, prefrontal cortex (BA9), anterior cingulate cortex (BA24), hypothalamus, pituitary gland, and testis, as well as regions such as the basal ganglia, caudate nucleus, and amygdala. These findings further reveal the potential regulatory roles of these genes in neurological and endocrine functions (Fig. 4B and 365 Additional file 2 Table S10).

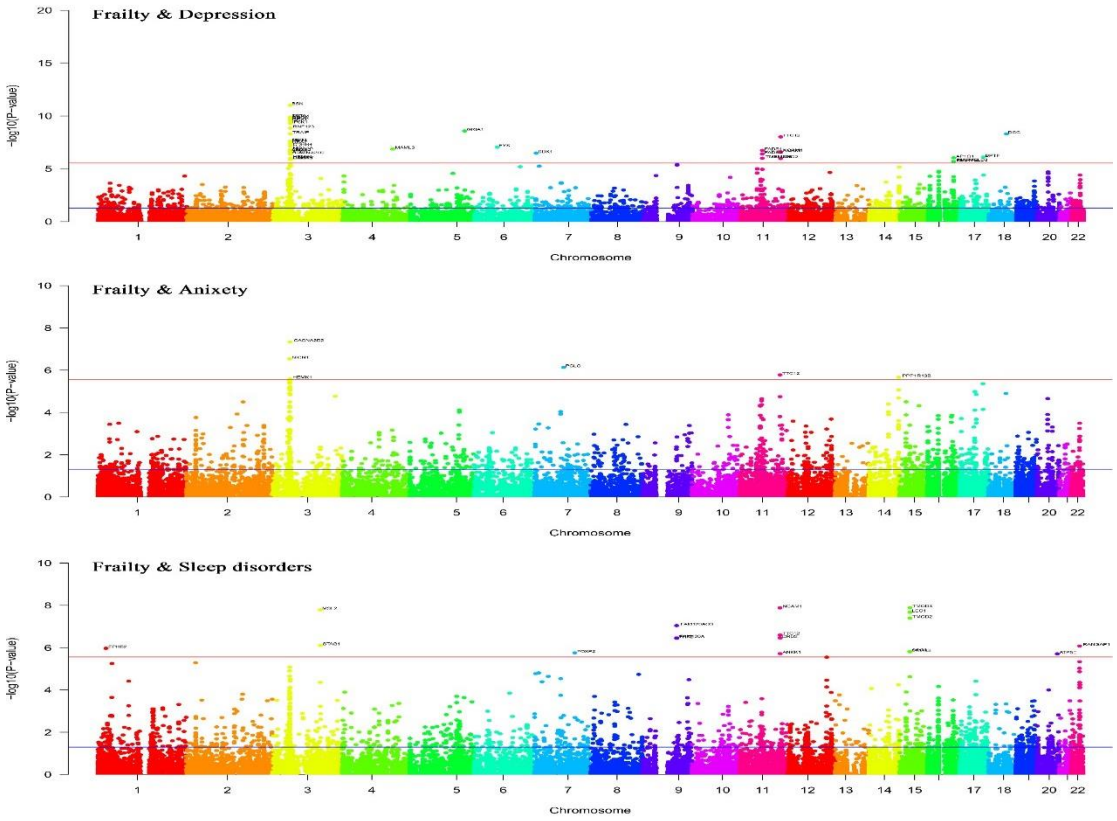

Fig. 4 Manhattan plot of MAGMA gene analysis. Note: Red dot lines represent the Bonferroni significant threshold (P < 0.05/18,294) and the significant genes were labeled

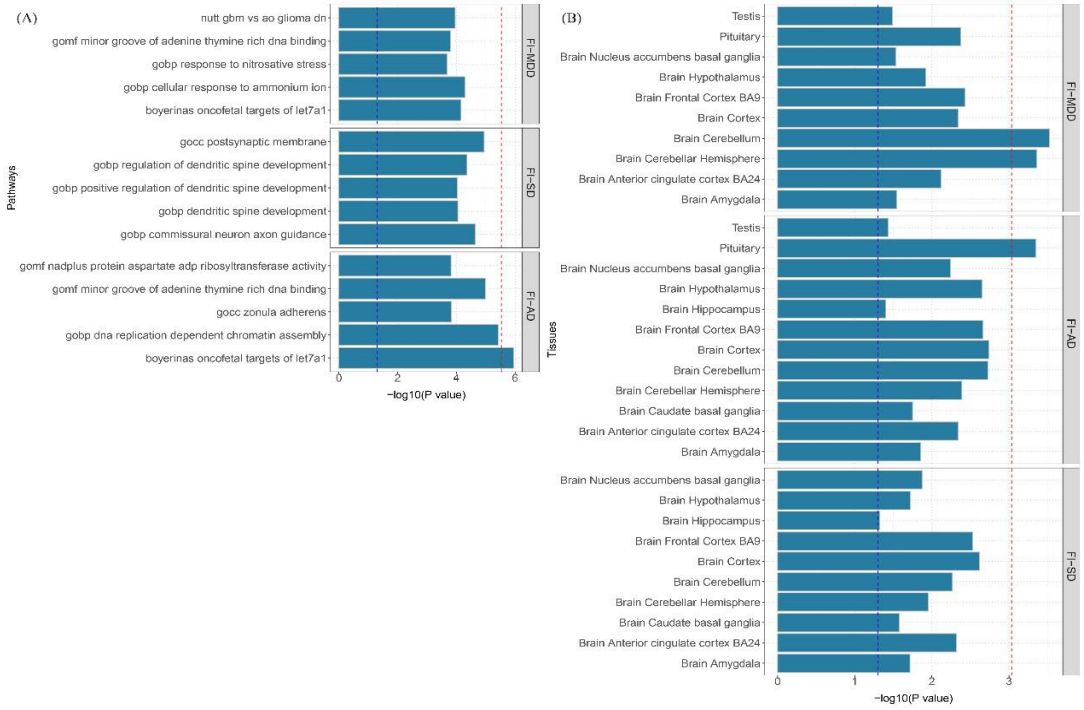

Fig. 5 Bar plot of MAGMA gene-set (A) and tissue-specific (B) analysis for genome-wide pleiotropic results. Note: The red dotted line represents the significance of 0.05 after multiple corrections, and the blue represents the significance of 0.05. Abbreviations: FI frailty, MDD depression, AD anxiety, SD sleep disorders

European population drug targets

By integrating SMR (p_SMR < 0.05, p_HEIDI > 0.5) based on eQTL data with PLACO, FUMA and MAGMA analysis results, we comprehensively identified 52 significant pleiotropic gene targets with potential drug development value in complex signals (Fig. 5), Furthermore, we verified the specific positions of these genes on chromosomes and their target functions by precise annotation (Additional file 2 Table S11 and Table S12). Among these, the *TTC12* gene exhibited strong genetic associations across all traits examined in this study. Additionally, within four reference drug target databases, the *AMT* gene showed significant associations with frailty and depression, while the *TMOD2* gene demonstrated a strong correlation with frailty and sleep disorders.

Immuno-colocalization analysis

Previous studies have demonstrated that multiple organs within the endocrine system play pivotal roles in regulating immune function. During immune responses, the hypothalamus and pituitary gland interact with the hypothalamic-pituitary-adrenal (HPA) axis to modulate inflammatory reactions and maintain immune balance, thereby influencing the onset and progression of various diseases. Building on this understanding, our study integrated GWAS data from 731 immune cell types and utilized the HyPrColoc method to analyze colocalization signals between frailty and three psychiatric disorders. This approach identified immune cell types with shared causal variants (Additional file 2 Table S13). The analysis revealed seven pleiotropic loci (*rs9812579, rs4619804, rs13090388, rs6446272, rs4466874, rs59034682,* and *rs2172969*) that strongly support the roles of three unique immune cell types in frailty and multiple psychiatric disorders. Specifically, the results highlight the immunomodulatory roles of *CCR2* on myeloid dendritic cells (DC), *SSC-A* on natural killer T (NKT) cells, *CD27* on IgD-CD38br cells, *CD45* on Gr MDSCs, and *CD20-CD38-* lymphocyte subsets, including *CD20-CD38-* AC and *CD20-CD38-* B cells, in the pathology of frailty and psychiatric disorders. These findings underscore the importance of potential immunological mechanisms in disease associations and provide insights into shared immune-mediated pathways.

Discuss

This study systematically investigates the shared genetic architecture between frailty and three types of psychiatric disorders, uncovering potential genetic associations and their underlying biological mechanisms. These findings enhance our understanding of the common pathological basis of these complex traits, offering critical insights into their interconnected etiology. Furthermore, the results provide valuable guidance for developing targeted and precise interventions for these conditions in the future.Through genetic association analysis, this study revealed a significant genetic correlation between frailty and three types of psychiatric disorders, providing strong evidence to support the hypothesis of shared genetic mechanisms underlying these conditions. Furthermore, HDL analysis indicates that patients with psychiatric disorders are at an increased risk of frailty progression, aligning with findings from previous observational studies[10,37–39]. For instance, a follow-up analysis of 8,108 patients with frailty demonstrated a positive correlation between depressive symptoms and frailty in both middle-aged individuals (45–59 years, n = 4,996) and older adults (≥60 years, n = 3,112), with

both groups showing highly consistent trajectories in depressive symptoms and frailty progression[40]. Additionally, a meta-analysis of 21 observational studies investigating the association between frailty and anxiety revealed that frail elderly individuals are significantly more likely to experience anxiety symptoms compared to their healthy counterparts, with the risk of anxiety progressively increasing from pre-frailty to frailty stages[41]. Despite these findings, a comprehensive exploration of the genetic mechanisms underlying these associations remains absent in the current literature, particularly at the gene and base-pair levels, where most studies remain descriptive. To address this gap, the present study systematically screened relevant genes and genetic variants using GWAS databases and derived the following conclusions.

This study systematically identified a series of genetic risk loci associated with psychiatric disorders and frailty using the PLACO method. Among these, loci such as *rs12635614*, *rs3752769*, and *rs536445* demonstrated significant associations between frailty and various psychiatric disorders. Existing research has highlighted the critical roles of these loci in disease development. For instance, *rs536445* has been shown to exhibit significant genetic pleiotropy in studies investigating migraine and headache associated with type 2 diabetes[42]. Moreover, *rs12635614* shows a significant correlation with unipolar depression and insomnia[43–45], while *rs3752769* is significantly associated with drug use assessment[46]. Notably, this study is the first to uncover the pleiotropic function of *rs3752768* in frailty and three types of psychiatric disorders.Through colocalization analysis of SNP loci, this study identified that the genomic region 3q26.31 is significantly associated with both frailty and the three psychiatric disorders. This region, located on chromosome 3, includes key genes such as *NLGN1*. *NLGN1* encodes a cell surface protein that facilitates cell-cell interactions by binding to members of the neurexin family. It is essential for synaptic function and signaling, potentially exerting its effects by recruiting and clustering other synaptic proteins. In vitro studies suggest that it triggers the re-formation of presynaptic structures and contributes to the specialization of excitatory synapses. Additionally, *NLGN1* plays a crucial role in maintaining the quality of wakefulness, as well as the synchronization of cortical activity during both wakefulness and sleep. This protein is also critical for 480 nervous system development[47].

This study identified a series of potential drug gene targets, including *TTC12*, *TMOD2*, and *AMT*, through multiple screening methods (SMR, PLACO, FUMA, and MAGMA). These genes exhibit strong pleiotropic effects. *TTC12* is part of a gene cluster associated with dopamine signaling pathways and plays a critical role in regulating the expression and function of dopamine receptors[48], particularly the D2 receptor, which influences reward and emotion regulation pathways[49]. Abnormal expression of *TTC12* has been linked to an increased risk of anxiety and depression, as well as significantly reduced sleep quality. Dysregulation of dopamine levels and neurotransmitter imbalances may also contribute to neurodegenerative diseases, further accelerating frailty progression[50].Inhibition of *TMOD2* has been identified as a key factor in the reduction of glutamate synapses and weakened excitatory synaptic transmission[51]. Glutamate, the primary excitatory neurotransmitter, enhances neural activity by activating AMPA and NMDA receptors. Reduced receptor function or expression impairs synaptic transmission, exacerbating anxiety symptoms. Notably, certain antidepressants, such as ketamine, restore glutamate transmission by enhancing NMDA receptor activity, further underscoring its importance in mood regulation[52]. Additionally, the balance between glutamate and the inhibitory

neurotransmitter GABA is essential for normal sleep[53]. Impaired glutamate transmission can disrupt this balance, leading to sleep disorders. Dysfunction of glutamate may also weaken motor nerve excitation, contributing to muscle weakness and increased fatigue.

AMT encodes a key enzyme in the one-carbon metabolic pathway, primarily involved in methyl transfer during glycine cleavage, and is closely linked to nervous system metabolism and energy regulation[54]. Inhibition of *AMT* function may influence the pathological processes underlying anxiety, depression, sleep disorders, and frailty through its role in metabolic regulation. In frail patients, energy metabolism disorders are often accompanied by reduced physical capacity and increased fatigue. The mitochondrial activity of *AMT* is also closely tied to oxidative stress and energy homeostasis. Targeting *AMT* may protect neurons by mitigating oxidative stress, thereby alleviating symptoms of depression and anxiety. Furthermore, *AMT* may indirectly contribute to sleep disorders by disrupting the balance between glutamate and GABA, further emphasizing its central role in multiple pathological processes. This study highlights the significant roles of *TTC12*, *TMOD2*, and *AMT* in the shared pathological mechanisms underlying psychiatric disorders and frailty, from both genetic and functional perspectives. These findings offer new insights and theoretical foundations for future precision therapies targeting these conditions.

The endocrine system regulates hormonal signaling through the autonomic nervous system (ANS), thereby influencing metabolism and energy balance[55]. In pathological studies of frailty and depression, this regulation is often disrupted by abnormal hypothalamic-pituitary-adrenal (HPA) axis function. Key features of this dysfunction include elevated levels of thyroid-stimulating hormone (TSH), decreased levels of free triiodothyronine (FT3), and a reduced FT3/free thyroxine (FT4) ratio[56]. Additionally, aging affects the pituitary gland, a critical organ that secretes growth hormone (GH) to stimulate the liver's production of insulin-like growth factor-1 (IGF-1)[57]. IGF-1 plays an essential role in promoting neuronal plasticity and enhancing skeletal muscle strength, thereby counteracting age-related physical degeneration[58,59]. IGF-1 also regulates the expression of inflammation- and autophagy-related genes through specific transcription factors such as DAF-16, contributing to frailty mechanisms[60]. Under stress conditions, the HPA axis rapidly responds to pressure signals by activating the paraventricular nucleus (PVN) of the hypothalamus, which releases corticotropin releasing factor (CRF)[61]. CRF stimulates the pituitary to secrete adrenocorticotropic hormone (ACTH), which subsequently induces glucocorticoid (GC) secretion from the adrenal cortex. Glucocorticoids mobilize energy and suppress peripheral inflammatory responses, thereby influencing behavior and neuroendocrine function.

In the context of anxiety, neuroimaging studies have demonstrated heightened activation of the prefrontal-parietal network and the cingulate-insular network in highly anxious individuals during high-demand tasks[62]. This compensatory response may be a key mechanism for maintaining cognitive performance under stress. Through S-LDSC and MAGMA tissue enrichment analyses, this study found that SNP heritability and shared genes for frailty, depression, and anxiety are predominantly concentrated in the nervous and endocrine systems. These findings support the concept of a unified disease mechanism and provide critical evidence for uncovering the shared genetic basis of multiple psychiatric disorders.

Through MAGMA analysis, multiple pathways were identified as playing critical roles in the pathogenesis of the target diseases. For instance, both the **GOCC GABAergic synapse and GOBP gamma-aminobutyric acid (GABA)** signaling pathways involve GABA as an inhibitory neurotransmitter in the central nervous system, primarily associated with depression and anxiety[63]. Although direct evidence linking GABA to frailty is currently lacking, a longitudinal study observed a decline in GABA levels in the brains of healthy elderly individuals over time, suggesting that reduced GABA levels may contribute to functional decline during aging[64]. Additionally, pathways such as GOBP synapse assembly, GOBP synaptic signaling, and GOBP regulation of synaptic plasticity have been associated with mood regulation and sleep disorders[65,66]. These pathways represent distinct stages of neuronal synaptic function, including synapse formation, signal transmission, and plasticity regulation, emphasizing the continuity and synergy of synaptic functions in their formation, maintenance, and adaptive changes. During aging, declines in synaptic function can result in cognitive decline, reduced motor abilities, and decreased neuroplasticity, thereby exacerbating the onset and progression of frailty[67].

Further analysis of pathways enriched across various traits revealed that many inflammation-related pathways play significant roles in the pathophysiology of frailty and psychiatric disorders. For example, GOBP cell redox homeostasis involves the regulation of cellular redox states, while REACTOME formation of senescence563 associated heterochromatin foci (SAHF) addresses the formation of heterochromatin foci linked to cellular senescence[68]. Additionally, GOBP cellular response to lipoprotein particle stimulus highlights responses to lipoprotein particles, and GOBP arginine metabolic process and GOBP arginine catabolic process are involved in arginine metabolism and nitric oxide (NO) production[69–71]. These findings suggest that inflammation and oxidative stress are important components of the shared pathophysiological mechanisms underlying frailty and psychiatric disorders. Through the analysis of previously identified pathways, this study revealed that several pathways are closely linked to inflammation, including the regulation of complement activation and its associated cell lysis, cellular responses to lipoprotein stimulation, arginine metabolism, and cellular mechanisms that inhibit viral transcription and inflammatory responses. Additionally, significant genetic enrichment of SNPs and genes was observed in the hypothalamus and pituitary regions, indicating that neuroinflammation can activate the HPA axis, which plays a critical role in the development of frailty and psychiatric disorders. Excessive activation of the HPA axis, leading to increased cortisol secretion, may trigger metabolic disorders and neural dysfunction[72,73]. Dysregulated inflammatory responses may further result in hippocampal neuron loss, impairing the negative feedback regulation of the glucocorticoid system, thereby exacerbating inflammation and accelerating the 582 progression of frailty[74].

To gain a deeper understanding of the shared mechanisms between frailty and psychiatric disorders, this study identified several immune cell markers through immuno-colocalization analysis, including *CCR2* on myeloid dendritic cells (DC), *SSC-A* on natural killer T (NKT) cells, *CD27* on IgD-CD38br cells, *CD45* on Gr myeloid-derived suppressor cells (MDSC), and *CD20-CD38-* lymphocyte subsets, including %lymphocyte, AC, and %B cell. Notably, *CCR2* plays a pivotal role in the migration and functional regulation of myeloid dendritic cells, influencing disease progression by modulating the

inflammatory environment[75]. The recruitment of myeloid cells to the central nervous system (CNS) via *CCR2* may contribute to the development of neurodegenerative diseases such as multiple sclerosis[76,77]. Moreover, the role of *CCR2* in immune responses is closely associated with depression, anxiety, and cognitive decline[78]. Chronic low-grade inflammation, a key pathological feature of these conditions, aligns with *CCR2*-mediated activation and migration of myeloid dendritic cells, further exacerbating inflammatory states.

The findings related to the GOBP Regulation of Complement-Dependent Cytotoxicity pathway (associated with complement activation and cell lysis) and the **GOBP Arginine Metabolic Process pathway** (involved in arginine metabolism and inflammation) suggest that *CCR2*-regulated inflammatory mechanisms may influence the metabolic activity and immune responses of myeloid dendritic cells through arginine metabolism[79]. Additionally, *CD45*-related markers identified in this study are crucial for the function and survival of Gr MDSCs[80]. These cells regulate complement604 dependent cytotoxicity, which may protect the tumor microenvironment or suppress autoimmune reactions. Dysfunction in this pathway could lead to chronic inflammation. Gr MDSCs may also indirectly affect synaptic plasticity by inhibiting neuroinflammation-induced neuronal damage, consistent with the GOBP Regulation of Synaptic Plasticity pathway, which directly modulates synaptic function and is closely linked to the HPA axis's negative feedback mechanism and inflammation-driven nerve damage[81].

Finally, *CD20-CD38-* %lymphocyte, %B cell, and AC immune cells identified in this study may represent cells in a unique developmental stage, such as immature, inactive, or early differentiation states. While these cells appear to play a role in the immune mechanisms linking frailty and psychiatric disorders, their specific functions require further investigation[82].

In summary, this study comprehensively investigates the shared genetic foundation and multi-layered biological mechanisms connecting frailty with three types of psychiatric disorders. Through the integration of genetic analysis, functional annotation, and immune cell colocalization, it offers a detailed understanding of the cross-mechanisms linking these complex traits. The findings provide critical insights into the intertwined pathophysiology of frailty and psychiatric disorders, establishing a solid theoretical basis for advancing future precision medicine approaches.

Limitation

This study has several limitations. First, the use of aggregated data, rather than individual-level data, limits the ability to perform more detailed population stratifications, such as gender, age, or other demographic characteristics. Second, the GWAS sample size for immune cells analyzed was relatively small, which may affect the reliability of the findings related to immune cell involvement and warrants cautious interpretation. Third, the analysis was restricted to individuals of European ancestry, which could constrain the applicability of the results to other populations or ancestries. Lastly, the relatively limited sample size of the frailty cohort may have reduced the statistical power, underscoring the need for careful consideration when interpreting the conclusions.

Conclusions

Our research unveils the intricate shared genetic architecture between frailty and 636 multiple psychiatric disorders, including depression, anxiety, and sleep disorders. Through comprehensive analysis, we identified pleiotropic risk loci (*rs536445*, *rs12635614*, *rs3752769*, and *rs3752768*), key genes (*TTC12*, *TMOD2*, and *AMT*), and critical pathways such as **GOCC GABAergic Synapse**, **GOBP Regulation of Synaptic Plasticity**, and **GOBP Arginine Metabolic Process**. These findings suggest that these diseases may share common mechanisms involving synaptic function regulation, inflammatory responses, and neurotransmitter imbalances. Additionally, tissues and organs significantly associated with these traits—including the cerebral cortex, hypothalamus, pituitary, and amygdala—highlight the central roles of the nervous and endocrine systems in the shared pathophysiology of frailty and psychiatric disorders. Colocalization analysis further revealed that immune cell types, such as myeloid dendritic cells and B cells, mediate disease progression by regulating the inflammatory environment and HPA axis activity. Our findings provide compelling evidence of a significant genetic association between frailty and psychiatric disorders, offering new insights into their shared genetic and biological foundations and presenting important clues for future precision medicine strategies.

Abbreviations

ACTH: Adrenocorticotropic Hormone
ANS: Autonomic Nervous System
AX: Anxiety Disorder
CNS: Central Nervous System
CRF: Corticotropin-Releasing Factor
CRP: C-Reactive Protein
DC: Dendritic Cells
DEGs: Differentially Expressed Genes
eQTL: Expression Quantitative Trait Loci
FT3: Free Triiodothyronine
FT4: Free Thyroxine
FUMA: Functional Mapping and Annotation Tool
GABA: Gamma-Aminobutyric Acid
GC: Glucocorticoids
GH: Growth Hormone
GOCC: Gene Ontology Cellular Component
GOBP: Gene Ontology Biological Process
Gr MDSCs: Granulocytic Myeloid-Derived Suppressor Cells
GWAS: Genome-Wide Association Study
HDL: High-Definition Likelihood
HEIDI: Heterogeneity in Dependent Instrument Test
HPA: Hypothalamic-Pituitary-Adrenal Axis
HyPrColoc: Hypothesis Prioritization for Multi-Trait Colocalization 677 IGF-1: Insulin-like Growth Factor-1

IL-6: Interleukin-6

IVW: Inverse Variance Weighting

LDSC: Linkage Disequilibrium Score Regression

LD: Linkage Disequilibrium

MAGMA: Multi-marker Analysis of Genomic Annotation

MAF: Minor Allele Frequency

MDD: Major Depressive Disorder

MDSC: Myeloid-Derived Suppressor Cells

MSigDB: Molecular Signatures Database

NKT: Natural Killer T Cells

NO: Nitric Oxide

PLACO: Pleiotropy Analysis under Composite Null Hypothesis

PVN: Paraventricular Nucleus

S-LDSC: Stratified Linkage Disequilibrium Score Regression

SAHF: Senescence-Associated Heterochromatin Foci

SD: Sleep Disorder

SE: Standard Error

SMR: Summary-based Mendelian Randomization

SNPs: Single Nucleotide Polymorphisms

TNF-α: Tumor Necrosis Factor-Alpha

TSH: Thyroid-Stimulating Hormone

Supplementary Information

Additional file 1:

Supplementary Methods and Fig. S1-S3. Supplementary Methods - A supplementary document on GWAS quality control, PLACO method, colocalization analysis, MAGMA analysis, HyPrColoc method, immune cell data description. Fig. S1. Manhattan plot of the PLACO results. Fig. S2. -QQ plots for pleiotropic results performed by PLACO. Fig. S3. Regional plots of each colocalized locus (PP.H4 > 0.7) identified for corresponding trait pair (FI&MDD) by using the PLACO. Fig. S4. Regional plots of each colocalized locus (PP.H4 > 0.7) identified for corresponding trait pair (FI&AD) by using the PLACO. Fig. S5. Regional plots of each colocalized locus (PP.H4 > 0.7) identified for corresponding trait pair (FI&SD) by using the PLACO.

Additional file 2:

Table S1. Data sources. **Table S2.** Genetic correlation analysis conducted by LDSC and HDL. **Table S3.** Identification of polymorphic risk SNP loci by using PLACO. **Table S4.** ANNOVAR category annotates leader SNP. **Table S5.** Colocalization analysis. **Table S6.** Shared pleiotropic loci among different trait pairs. **Table S7.** S-LDSC tissue specific. **Table S8.** Identification of significant pleio-tropic genes by using MAGMA. **Table S9.** MAGMA Gene-set analysis. **Table S10.** MAGMA tissue-specific

analysis. **Table S11.** European population drug targets. **Table S12.** Drug Target Annotation. **Table S13.** Multi-trait colocalization analysis highlighted key role of immune cells (PP>0.7).

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Authors' contributions

Zhijun Tian: Conceptualization, Data Curation, Formal Analysis, Writing-Original Draft, Writing-Review & Editing. Yudan Zhou: Formal Analysis, Writing-Original Draft. Mei Feng: Methodology, Writing-Original Draft. Ao Shen: Project Administration, Writing-Review & Editing. Duoer Mei: Resources, Writing-Original Draft. Huijia Luo: Writing-Original Draft. Hong Guo: Funding Acquisition, Methodology, Project Administration, Supervision, Writing-Review & Editing.

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Availability of data and materials

Data is available in public, open access repositories corresponding to the original studies (e.g., GWAS catalog).

Main codes used in our research are available at https:// github. com/ biost atYu/ MRcode/ tree/ main/ AD_ BALL.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

All authors declared no potential conflicts of interest.

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Appendices

Supplementary Methods

GWAS data QC

We removed all non-biallelic SNPs, SNPs with chain ambiguous alleles (A/T, C/G alleles), SNPs with MAF <1%, and SNPs without rs IDs, duplicate SNPs, and SNPs whose alleles does not match Phase 3 of the 1000 Genomes Project. Additionally, SNPs located in major histocompatibility complex (MHC, chr 6: 25–35 Mb) region were excluded from main analysis and annotations due to its complex LD structure.

Pleiotropic analysis under composite null hypothesis analysis (PLACO)

This method could detect pleiotropic signals by using summary-level association statistics between complex traits. Considering the potential correlation among autoimmune diseases, we calculated correlation matrix of Z-scores. Then a level-α IUT method was used to test pleiotropy hypothesis: H_0 is the null hypothesis, which could be expressed as $H_0 : H_{00} \cup H_{01} \cup H_{02}$, and alternative hypothesis H1 could be further expressed as:

$$\begin{aligned} &H_1 : H_{00}^a \cap H_{01}^a \cap H_{02}^a, \\ &\text{where } H_{00} : \beta_{AD} = \beta_{B-ALL} = 0, \\ &H_{01} : \beta_{AD} = 0,\ \beta_{B-ALL} \neq 0, \\ &H_{02} : \beta_{AD} \neq 0,\ \beta_{B-ALL} = 0. \end{aligned} \quad (1)$$

The H^a represents the complement of H. $\beta_{Disease}$ represents effect size of autoimmune diseases. The maximum of P values for testing H_0 vs H_1 were viewed as the final P values.

Bayesian colocalization analysis using coloc

The coloc package can be used to perform genetic colocalization analysis of two potentially related phenotypes to test whether they share common genetic causal variants in given regions. The approach assumes that each genetic variant is equally likely to affect gene expression or a trait, and is only interested in whether shared causal variants are plausible. For different combinations of the two phenotypes, the study offers five hypotheses: ***H₀***: No association with either trait; ***H₁***: Association with

autoimmune disorders, not with B-ALL; ***H_2***: Association with B-ALL, not with autoimmune disorders; ***H_3***: Association with autoimmune disorders and B-ALL, two independent SNPs; ***H_4***: Association with autoimmune disorders and B-ALL, one shared SNP. Therefore, H_4 assumes that the effects of shared variants on two traits are independent, while high PP_4 measures correlation, not causation.

MAGMA analysis

In MAGMA gene analysis, genetic marker data are aggregated to the gene level and converted from the association of test SNPs to the joint association of all markers in the test gene with the phenotype. The model for MAGMA gene analysis is based on the multiple linear principal component regression method, which uses the F test to calculate gene p-values. In order to ensure that the model is identifiable in the presence of highly collinear SNPs, the model projects the SNP matrix of the gene onto its principal component (PC). Then the PCs with very small eigenvalues were pruned, the remain PCs were viewed as predictor factors for phenotypes in the linear regression model. Likewise in MAGMA gene set analysis, individual genes are aggregated into genomes with certain biological, functional, or other characteristics. This aggregation has the advantage of greatly reducing the number of association tests that need to be performed and can detect effects consisting of multiple weak associations, greatly improving statistical power.

Multi-trait colocalization analysis using HyPrColoc

HyPrColoc is based on the similar statistical model as coloc, but unlike coloc, HyPrColoc uses summary statistics for a large number of traits to identify multi-traits colocalization association signals. This method accurately approximates the posterior probability of colocalization for a single causal variant by enumerating only a small number of putative causal associations (assuming that there is at most one causal variant per trait), avoiding repeated pairwise colocalization analyses, and identify co-localization signals between multiple traits efficiently and quickly. However, this method may increase the false negative rate and reduce the performance of identifying shared causal variants to some extent.

Detailed information of immune cells used in HyPrColoc analysis

The GWAS summary statistics for 731 immune traits could be publicly available in the GWAS Catalog (accession numbers from GCST0001391 to GCST0002121), of which 118 were absolute cell (AC) counts, 389 were median fluorescence intensities (MFIs) reflecting the levels of surface antigens, 32 were morphological parameters [MP, forward scatter (FSC) and side scatter (SSC), which are proportional to the cell volume, and intracellular complexity and the surface texture of cells, respectively], and 192 were relative cell (RC) counts. This GWAS analysis was conducted based on 3,757 European samples (57% women) to test around 22 million single nucleotide polymorphisms (SNPs) genotyped with high density arrays after adjusting for several covariates (i.e., sex, age, and age^2). Finally, these SNPs were imputed with a sequence-based reference panel.

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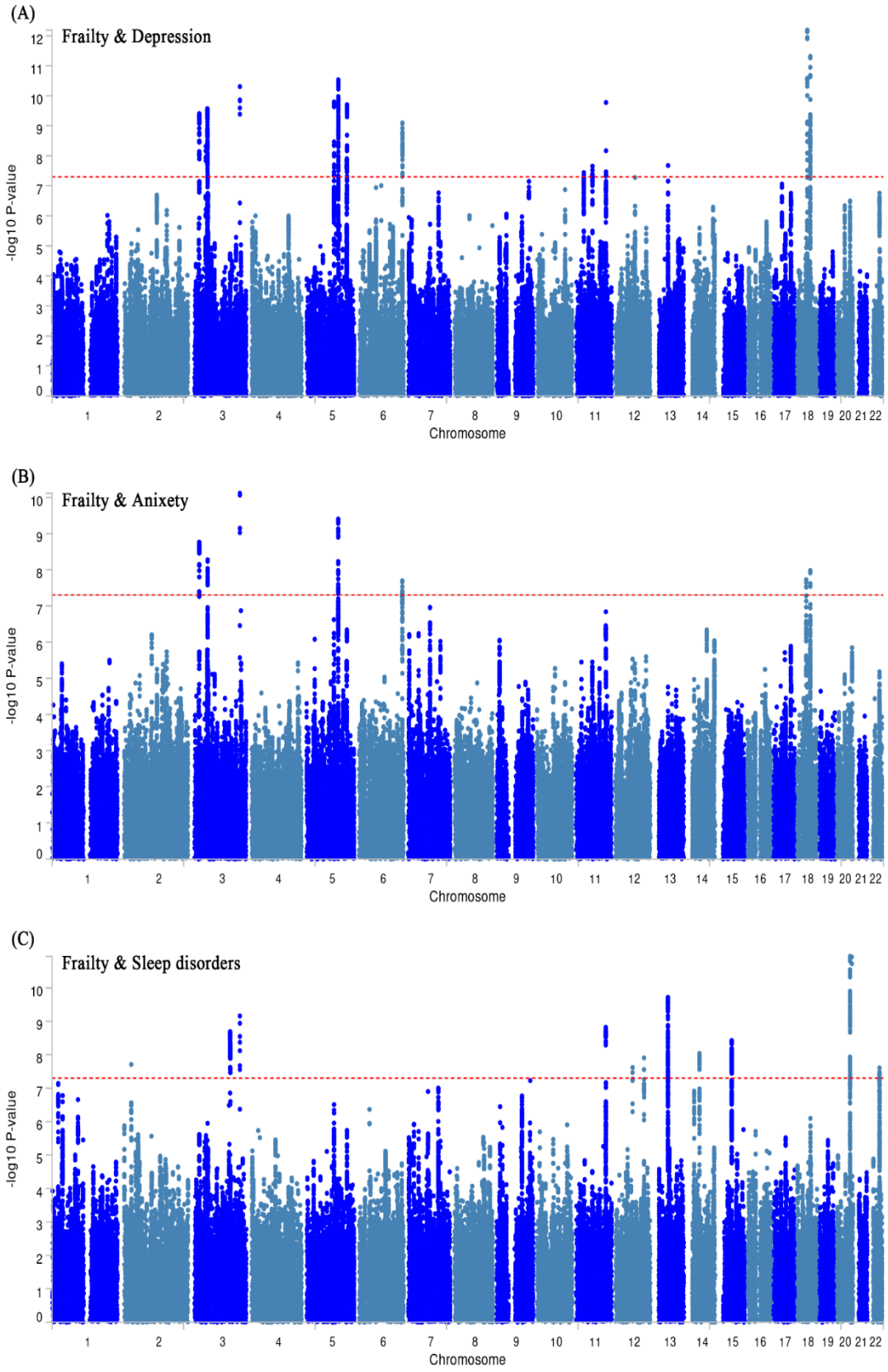

Supplementary Figures

Figure S1. Manhattan plot of the PLACO results. Note: Red line represents the significance of 5×10^{-8}.

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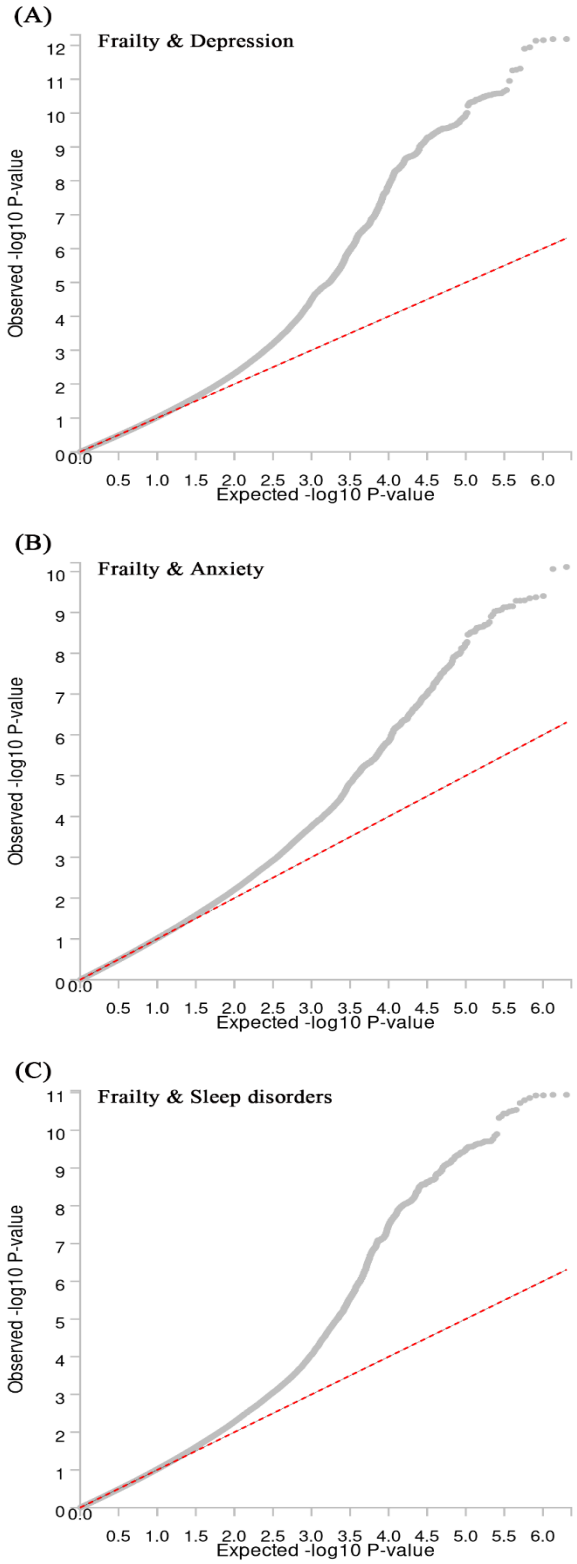

Figure S2. QQ plots for pleiotropic results performed by PLACO.

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Figure S3. Regional plots of each colocalized locus (PP.H4 > 0.7) identified for corresponding trait pair (FI&MDD) by using the PLACO. Note: PP.H4 was posterior probability of H4 calculated by coloc analysis; SNPs in LD that do not have any significant independent lead SNPs in the selected region are grayed out. For genes, mapped genes drawn by position mapping are in red; blue are unmapped protein-coding genes; dark gray are unmapped non-coding genes. Abbreviations: FI, frailty; MDD, depression.

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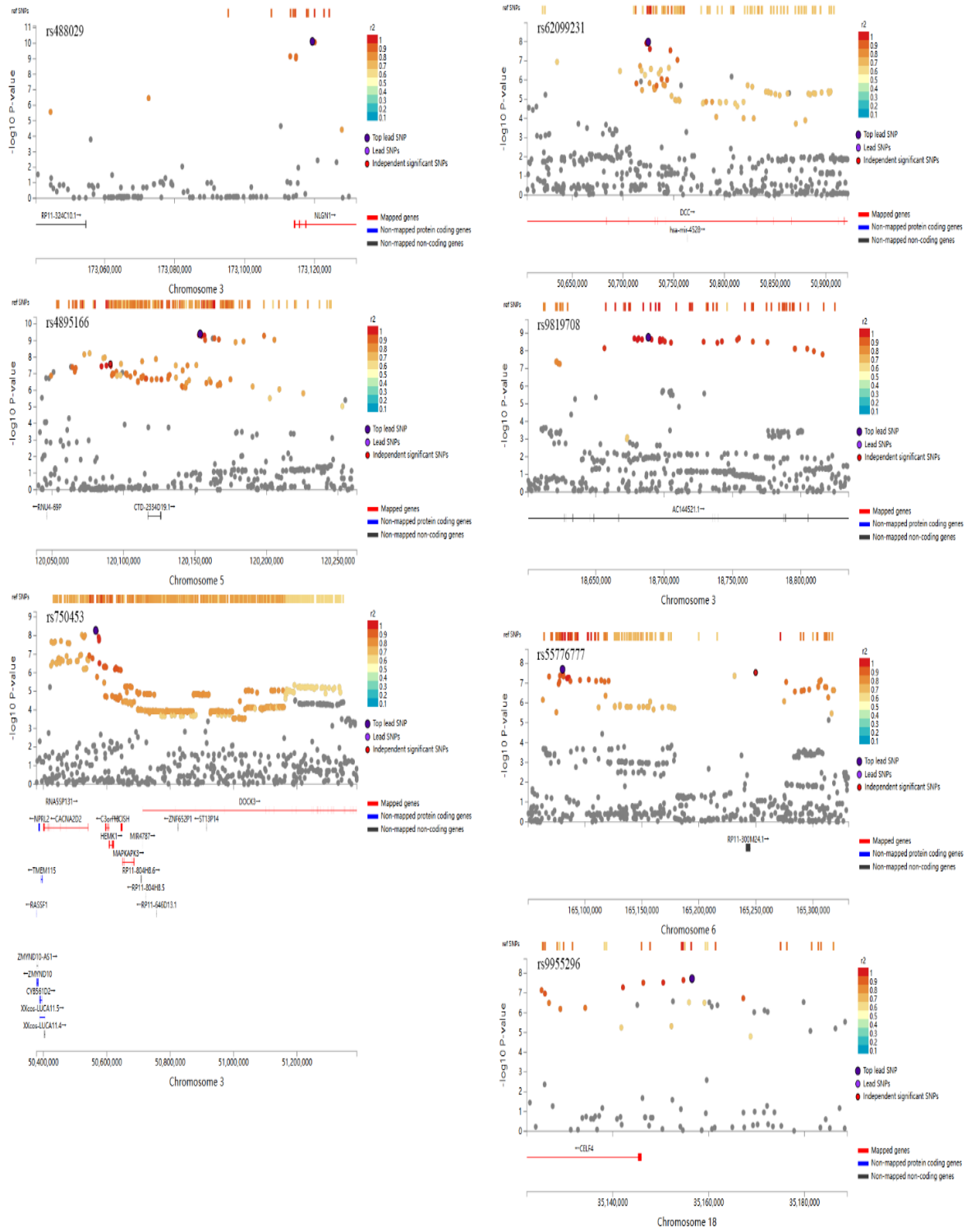

Figure S4. Regional plots of each colocalized locus (PP.H4 > 0.7) identified for corresponding trait pair (FI&AD) by using the PLACO. Note: PP.H4 was posterior probability of H4 calculated by coloc analysis; SNPs in LD that do not have any significant independent lead SNPs in the selected region are grayed out. For genes, mapped genes drawn by position mapping are in red; blue are unmapped protein-coding genes; dark gray are unmapped non-coding genes. Abbreviations: FI, frailty; AD, anxiety.

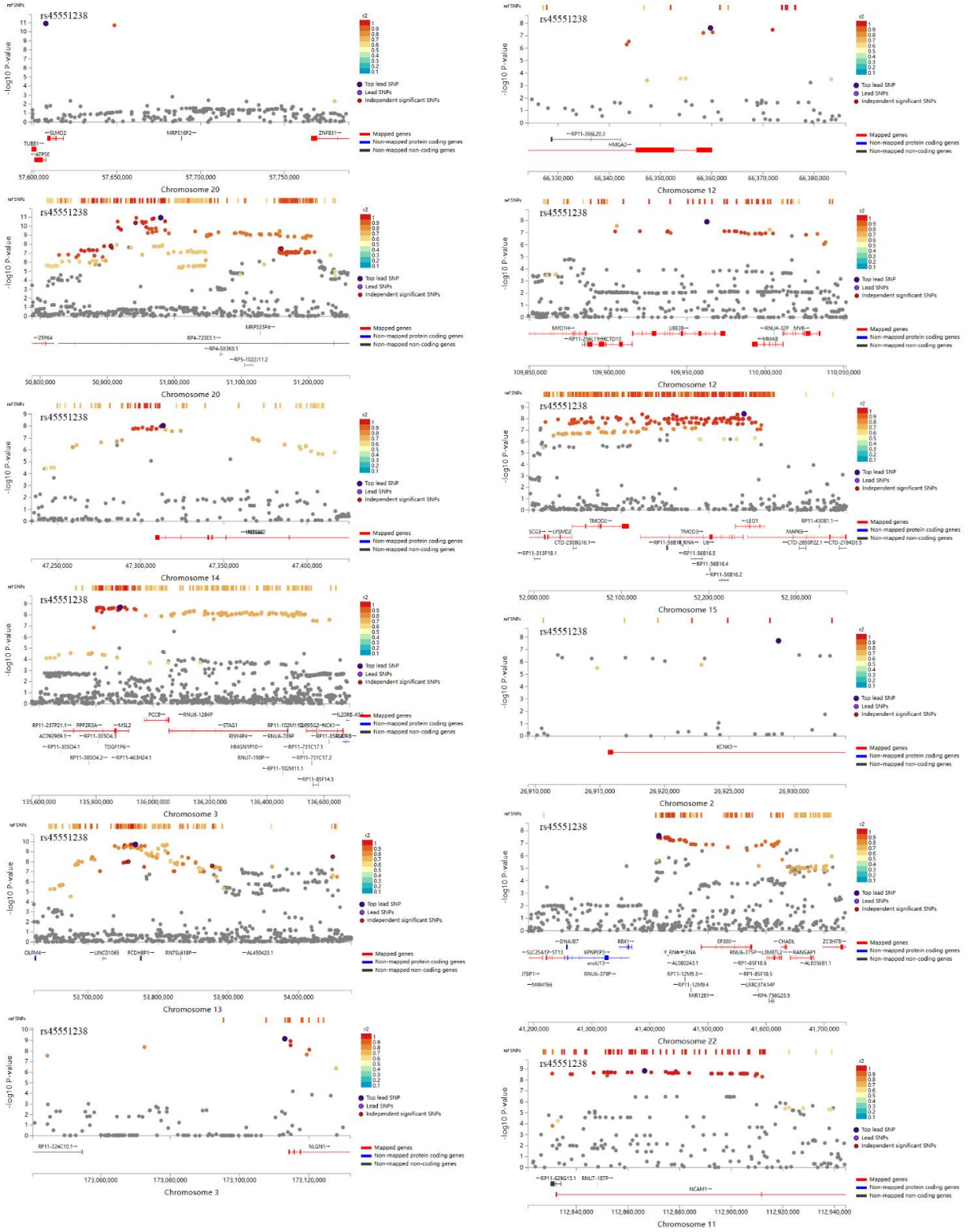

Figure S5. Regional plots of each colocalized locus (PP.H4 > 0.7) identified for corresponding trait pair (FI&SD) by using the PLACO. Note: PP.H4 was posterior probability of H4 calculated by coloc analysis; SNPs in LD that do not have any significant independent lead SNPs in the selected region are grayed out. For genes, mapped genes drawn by position mapping are in red; blue are unmapped protein-coding genes; dark gray are unmapped non-coding genes. Abbreviations: FI, frailty; SD, Sleep disorders.