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Shared genetic liability between major depressive disorder and osteoarthritis

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Aims

Deciphering the genetic relationships between major depressive disorder (MDD) and osteoarthritis (OA) may facilitate an understanding of their biological mechanisms, as well as inform more effective treatment regimens. We aim to investigate the mechanisms underlying relationships between MDD and OA in the context of common genetic variations.

Methods

Linkage disequilibrium score regression was used to test the genetic correlation between MDD and OA. Polygenic analysis was performed to estimate shared genetic variations between the two diseases. Two-sample bidirectional Mendelian randomization analysis was used to investigate causal relationships between MDD and OA. Genomic loci shared between MDD and OA were identified using cross-trait meta-analysis. Fine-mapping of transcriptome-wide associations was used to prioritize putatively causal genes for the two diseases.

Results

MDD has a significant genetic correlation with OA (r_g = 0.29) and the two diseases share a considerable proportion of causal variants. Mendelian randomization analysis indicates that genetic liability to MDD has a causal effect on OA (b_{xy} = 0.24) and genetic liability to OA conferred a causal effect on MDD (b_{xy} = 0.20). Cross-trait meta-analyses identified 29 shared genomic loci between MDD and OA. Together with fine-mapping of transcriptome-wide association signals, our results suggest that Estrogen Receptor 1 (*ESR1*), SRY-Box Transcription Factor 5 (*SOX5*), and Glutathione Peroxidase 1 (*GPX1*) may have therapeutic implications for both MDD and OA.

Conclusion

The study reveals substantial shared genetic liability between MDD and OA, which may confer risk for one another. Our findings provide a novel insight into phenotypic relationships between MDD and OA.

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Keywords: Major depressive disorder, Osteoarthritis, ESR1, Mendelian randomization, SOX5, GPX1

Article focus

- We aim to investigate mechanisms underlying relationships between major depressive disorder (MDD) and osteoarthritis (OA) in the context of common genetic variations.

Key messages

- Our results indicate that the two diseases have a close genetic correlation and share considerable causal variants.
- Our Mendelian randomization analysis indicated that genetic liability to MDD and OA confers risk for one another.
- Cross-trait meta-analyses identified 29 shared genomic loci between MDD and OA.
- Together with fine-mapping of transcriptome-wide association signals, our results suggest Estrogen Receptor 1 (*ESR1*), SRY-Box Transcription Factor 5 (*SOX5*), and Glutathione Peroxidase 1 (*GPX1*) as promising risk genes for MDD and OA, which may inform treatment regimens for patients who have both diseases.

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Strengths and limitations

- We employed multiple analytic frameworks to systematically elucidate the genetic relationships between MDD and OA.
- Transcriptome-wide association study associations may potentially contain noises, since the gene expression levels were imputed from weighted linear combinations of single-nucleotide polymorphisms.

Introduction

Major depressive disorder (MDD) is characterized by persistent low mood and is the most prevalent mental disorder accompanied by considerable morbidity, mortality, and high risk of suicide.[1] It confers a heavy burden on society, not only due to its high prevalence, but also because of the high comorbidity with other medical outcomes,[2] which further worsens the outcome of other health problems and increases mortality. Long-term depression generally adds to the risk for somatic illness, while chronic somatic diseases are frequently accompanied by depression.[3]

Osteoarthritis (OA) is the most common musculoskeletal disease worldwide, and a leading cause of pain and disability in older adults.[4] OA is characterized by progressive cartilage loss, osteophyte formation, and subchondral sclerosis, leading to a large amount of pain and disability in the elderly worldwide.[5] A major genetic component to OA risk has been demonstrated by epidemiological studies.[6] OA pain and associated disability may increase the risk for MDD through both biological and psychological mechanisms.[7] Chronic pain leads to decreased brain volume, specifically for mood regulation,[8] and the disability resulting from knee OA may result in psychological changes relevant to depression. According to a report from 2015, approximately 21% of adults with OA coexist with depression.[9] OA patients coexisting with depression report higher healthcare costs, and use pain medication more frequently than those without depression.[9,10]

Although previous studies have detected associations between MDD and OA, key questions remain: 1) to what extent do the two conditions share genetic influences?; 2) are the associations driven by aetiologically causal effects?; and 3) what potential biomarkers or mechanisms may underline these associations?

A genetic correlation coefficient is a prevailing measure to qualify the genetic relationship between two traits. The sign of the correlation coefficient indicates directions of the shared genetic effects. However, genetic correlation analyses may be underpowered in dealing with mixtures of effect directions across shared genetic variants.[11] Polygenic overlap was recently proposed to measure the fraction of genetic variants causally associated with both traits over the total number of causal variants across a pair of traits involved.[11] Frei et al[11] introduced a novel statistical framework (MiXeR) to quantify polygenic overlap irrespective of genetic correlation between traits. In the MiXeR pipeline, the total number of shared and trait-specific causal variants across a pair of traits is quantified.

Mendelian randomization (MR) is an analytic framework that uses genetic variants as instrumental variables to test for causative association between an exposure and an outcome.[12] MR is efficient and cost-effective for large datasets curated from genome-wide association studies (GWASs). Recently, GSMR has been developed by leveraging power from multiple genetic variants accounting for linkage disequilibrium (LD) between the variants.[13]

In this study, we estimated genetic correlation and polygenic overlap between MDD and OA. Pleiotropic genomic loci shared between MDD and OA were identified using cross-trait meta-analyses. We further performed a multi-single-nucleotide polymorphism (SNP) MR analysis on summary results presented in GWAS datasets to test the causal associations between MDD and OA. In addition, we explored potential biological mechanisms underlying the phenotypic relationships between the two diseases.

Methods

GWAS summary datasets and quality control. This study relied on deidentified summary-level data that have been made publically available, and part of the MDD dataset was obtained by approval from 23andMe.[14] Ethical approval had been obtained in all original studies. The MDD dataset includes 135,458 cases and 344,901 healthy controls,[15] and the OA dataset includes 77,052 cases and 378,169 healthy controls.[16] For each dataset, inclusion criteria include bi-allelic SNPs and imputation information above 0.9. Each SNP was compared between two traits and ambiguous SNPs were excluded. If a SNP was mapped in opposite strands in the two datasets, alleles of the SNP in the second dataset were flipped. Effect direction of a SNP was reversed for the second dataset if alleles of the SNP were reversed in the two datasets.

Genetic correlation and polygenic overlap analysis. GWAS summary results were used to analyze the genetic correlation of MDD with OA using linkage disequilibrium (LD) score regression.[17,18] Polygenic overlap was analyzed by MiXeR v1.2 (Norway) using default parameters.[11] The test statistics of MiXeR take into account effects of LD structure, minor allele frequency (MAF), sample size, cryptic relationships, and sample overlap. The total number of causal variants is reported as 22.6% of the total estimate, which accounts for 90% of SNP heritability for each trait.

MR analysis. Bidirectional causal associations between MDD and OA were inferred using generalized summary data-based Mendelian randomization (GSMR).[13] Instrumental variants were selected based on default $p \leq 5 \times 10^{-8}$. Pleiotropy is a potential source of bias that can lead to an inflated estimation in a MR analysis.[19] Therefore, pleiotropy evaluation for a large number of instrumental variants is critical. In GSMR, HEIDI-outlier offers a statistical approach to detect and eliminate genetic instruments

with apparent pleiotropic effects on both risk factors and disease.[13,20]

Cross-trait meta-analysis. We performed a cross-trait meta-analysis of the MDD with OA using the subset-based fixed-effects method ASSET v2.4.0, which permits the characterization of each SNP concerning its pattern of effects on multiple phenotypes.[21] The analysis results return a p-value and show the best subset containing the studies contributing to the overall association signal for each variant. The meta-analysis pools the effect of a given SNP across two studies, weighting the effects by the size of the study. After subset-based meta-analysis, SNPs for which two-tailed p-values were lower than 5×10^{-8} were considered statistically significant. Functional mapping and animation (FUMA) was used to map SNPs to genes and identify LD-independent genomic regions.[22]

To ensure that sample overlap did not contribute to inflated estimates of genetic overlap between MDD and the three traits, λmeta statistics were calculated.[23] The λmeta is a statistic that uses effect size concordance to detect sample overlap or heterogeneity. Under the null hypothesis, λmeta = 1 when the pair of cohorts are completely independent. When there are overlapping samples, λmeta < 1.

Fine-mapping of TWAS associations. To prioritize putatively causal genes, we used fine-mapping of causal gene sets (FOCUS v 0.6.10 (USA))[24] to the meta-analysis result of MDD and OA in the brain. FOCUS models predicted expression correlations and assign a posterior inclusion probability (PIP) for genes at each transcriptome-wide association study (TWAS) region and relevant tissue types. TWAS has been employed to identify risk genes for OA.[25] A multi-tissue expression quantitative trait loci (eQTL) reference weight database from the software was used as eQTL weights, and LD information from linkage disequilibrium score regression (LDSC) was used as reference.

Knowledge-based analysis. We obtained GWAS results (including meta-analysis) of depression (MDD and depressive symptoms) and OA from the GWAS Catalogue database.[26,27] Protein-protein interaction analysis was conducted using STRING v11 (Academic Consortium, ELIXIR, UK).[28] Specific expression analysis (SEA v1.1; Dougherty Lab, USA) was used to test whether the identified risk genes are over-represented by enriched expression in adult brain regions and development.[29,30] For each tissue, transcripts from the processed GTEx transcripts that are specifically expressed or enriched have been identified by using the SEA pSI R package function to calculate the specificity index probability (pSI).[29] The significance levels of shared genes between MDD and OA enriched in each tissue were identified by Fisher's exact test with Benjamini-Hochberg correction. We then explored whether the genes shared by MDD and OA have been implicated in previous genome-wide association studies. A detailed description of the methods is provided in the Methods section of the Supplementary File.

Statistical analysis. Statistical analyses were conducted using R 4.0.5 (R Foundation for Statistical Computing, Austria) or Python 3.8 environment. LD score regression was used to measure genetic correlation between MDD and OA. Bivariate causal mixture model was used to quantify polygenic overlap between MDD and OA. A p-value < 0.05 indicated that the difference was statistically significant.

Results

Genetic correlation and polygenic overlap analysis. Genetic correlation analyses indicated that MDD has a significant genetic correlation with OA ($r_g = 0.29$, standard error (SE) = 0.03, $p = 4.11 \times 10^{-30}$). Polygenic analysis indicated that 15,800 variants causally influence MDD and 8.9 K influence OA. Among these variants, 5.9 K are shared between the two diseases (Figure 1a).

MR analysis. MR analysis indicated that genetic liability of MDD conferred a causal effect on OA ($b_{xy} = 0.24$, s.e. = 0.04, $p = 2.36 \times 10^{-8}$, Figure 2a) and genetic liability of OA conferred a causal effect on MDD ($b_{xy} = 0.20$, s.e. = 0.05, $p = 2.74 \times 10^{-5}$, Figure 2b).

Cross-trait meta-analysis. The cross-trait meta-analysis of MDD and OA revealed 71 loci, 176 independent significant SNPs (IndSigSNPs), and 82 lead SNPs, including 51 pleiotropic IndSigSNPs located in 29 loci (associated with both traits) (Figure 1b, Table I, Supplementary Table i). A total of 75 pleiotropic protein-coding genes were identified, including 25 protein-coding genes which were implicated by the pleiotropic IndSigSNPs and 50 protein-coding genes located within the clumping range of independent significant SNPs (Supplementary Table ii). λmeta values were 1.17 for datasets between MDD and OA, indicating no significant overlap between MDD and the OA GWAS samples. Quantile-quantile (QQ) plots displaying the observed meta-analysis statistics, versus the expected statistics under the null model of no associations in the $-\log_{10}(p)$ scale, are shown in Supplementary Figure a.

Fine-mapping of TWAS associations. We used fine-mapping of TWAS associations to prioritize putatively causal genes from the meta-analysis of MDD and OA. A total of 81 gene-tissue pairs were identified as in the 90% credible set in the brain tissue, involving 80 genes (Supplementary Table iv). Nine genes in the credible set with high PIP (> 0.90) are shown in Table II.

Knowledge-based analysis. A total of 17 genes out of the 25 pleiotropic protein-coding genes have been identified in previous GWASs on depression or OA (Supplementary Table iii). At pSI threshold of 0.05, the 25 pleiotropic protein-coding genes were enriched in cortex (false discovery rate (FDR) = 0.007) and marginally enriched in striatum (FDR = 0.058) (Figure 2c). PPI analysis showed that most of the 75 genes were interconnected, constituting two large networks, with ESR1 being involved in one network and SOX5 being involved in another network (Figure 3).

Discussion

The comorbidity between depression and a myriad of health outcomes typically forms a vicious cycle, known

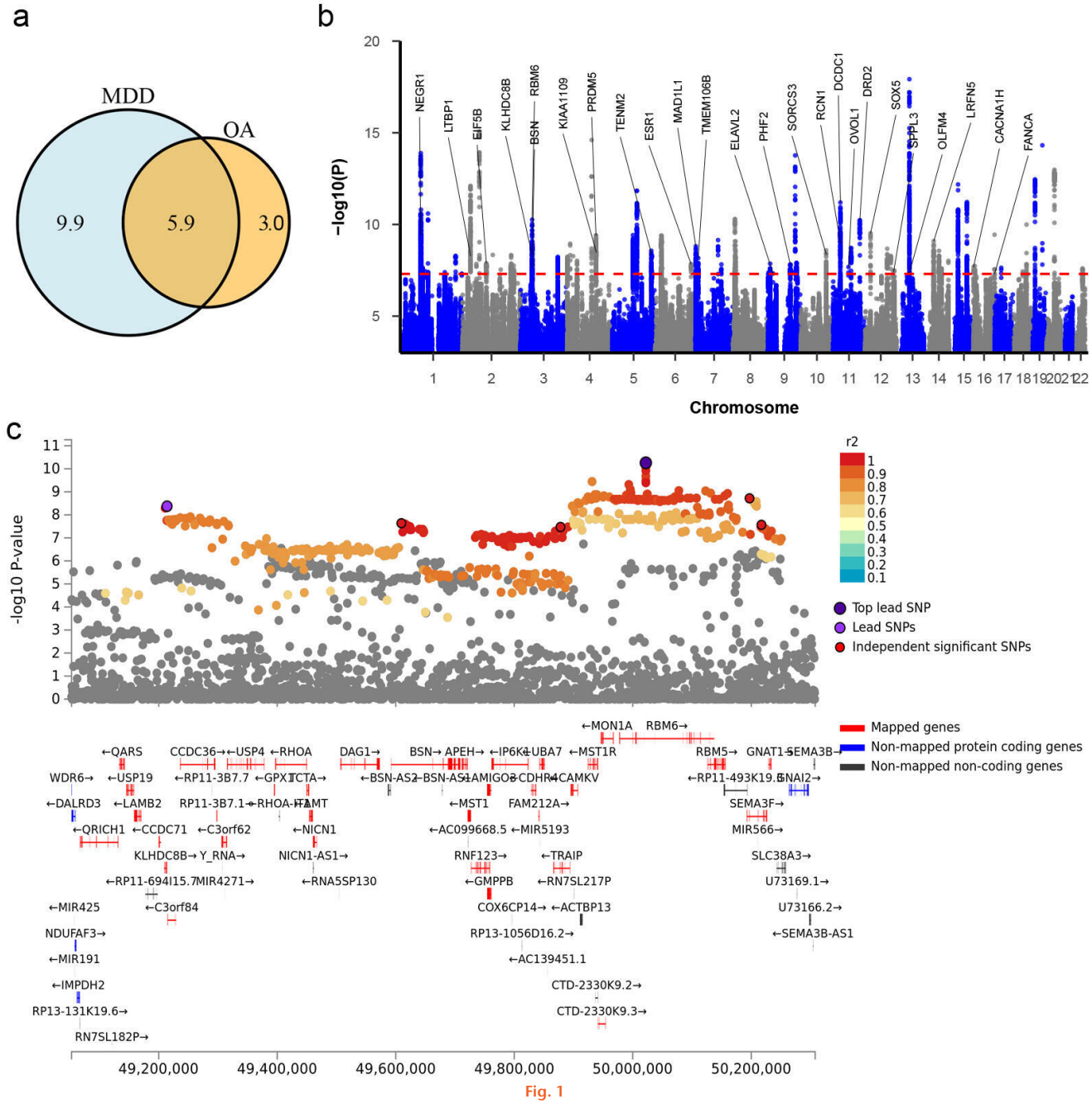

Fig. 1

Shared genetic liability between major depressive disorder (MDD) and osteoarthritis (OA). a) Venn diagrams of unique and shared polygenic components at the causal level, showing the polygenic overlap between MDD and OA. The numbers indicate the estimated quantity of causal variants (in thousands) per component, explaining 90% of single nucleotide polymorphism (SNP) heritability in each phenotype. The size of the circles reflects the degree of polygenicity. b) Manhattan plot of meta-analysis of MDD with OA. The x-axis is the chromosomal position of SNPs and the y-axis is the significance of the SNPs ($-\log_{10}$P). Protein-coding genes containing or adjacent to independent significant SNPs shared by two traits were annotated. c) A genomic locus shared by MDD and OA and implicated by fine-mapping of transcriptome-wide association signals.

to significantly impact the course and management of depression and its associated conditions. OA, the commonest form of arthritides, is one of the leading causes of functional disability and reduced quality of life worldwide, particularly in the elderly. A better understanding of the pathophysiology of OA is necessary to improve effective preventive strategies.

In this study, we detected a significant genetic correlation between MDD and OA (r = 0.29), higher than those between MDD and autism spectrum disorder (r = 0.16) and obsessive-compulsive disorder (r = 0.23).[31] More than half (66%) of causal variants influencing OA risk may also affect MDD. Our results indicate a higher polygenicity of MDD than OA. More importantly, we identified

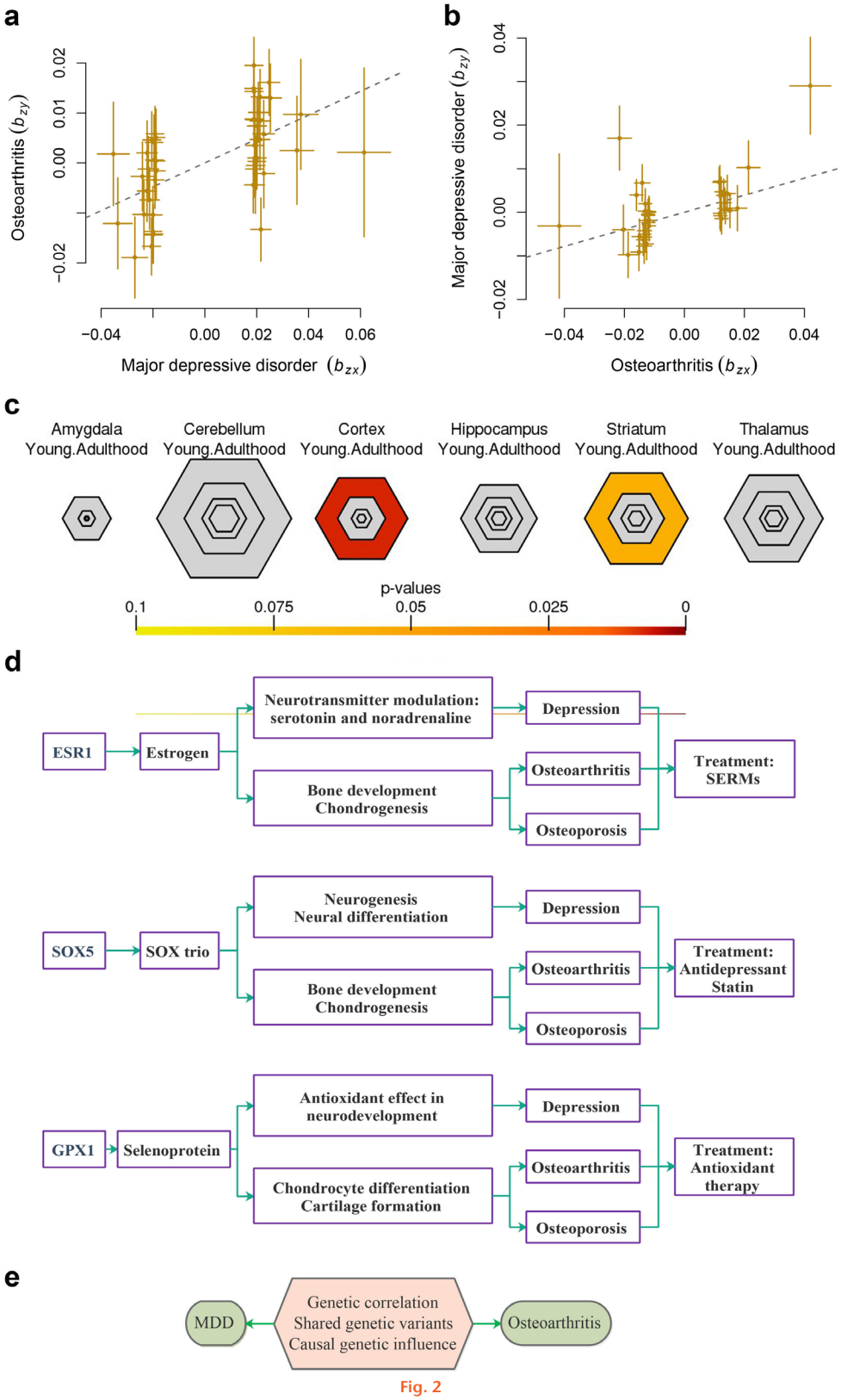

Fig. 2

The associations between major depressive disorder and osteoarthritis and specific expression analyses (SEA). a) and b) The causal associations between major depressive disorder (MDD) and osteoarthritis (OA). The lines denote effect sizes (b_{xy}). c) SEA of adult brain regions for the 25 shared genes. The significance of overlap of provided gene lists with transcripts enriched in specific cell types or tissue types is indicated by the intensity of colour. d) Schematic relationship between Estrogen Receptor 1 (ESR1) and SRY-Box Transcription Factor 5 (SOX5) and depression, OA, and osteoporosis. e) Genetic variation mediating associations between MDD and OA. SERMs, selective oestrogen receptor modulators.

Table I. Genomic loci shared between major depressive disorder and osteoarthritis.

Lead SNP	Chr:BP	p-value	Start:End	Genes
rs10789340	1:72,940,273	1.29×10^{-14}	72511514:74,077,588	NEGR1; RPL31P12; RP4-660H19.1; RP11-262K1.1
rs2061027	2:33,434,336	8.05×10^{-13}	33370457:33,464,969	LTBP1
rs6720885	2:99,971,289	1.30×10^{-8}	99573471:100,109,001	EIF5B
rs12471530	2:215,433,178	1.75×10^{-8}	215407397:215,481,251	AC107218.3
rs199956414	3:50,022,089	5.51×10^{-11}	49109919:50,250,837	KLHDC8B; BSN; RBM6; C3orf84
rs13143036	4:121,623,038	3.99×10^{-10}	121546342:121,655,414	PRDM5
rs45510091	4:123,186,393	3.26×10^{-9}	123122856:123,558,330	KIAA1109
rs1363104	5:103,917,797	1.46×10^{-12}	103671867:104,082,179	RP11-6N13.1
rs1549212	5:166,996,722	4.77×10^{-9}	166985224:167,055,936	TENM2
rs9479138	6:152,215,199	1.42×10^{-8}	152201201:152,264,529	ESR1
rs3823624	7:2,110,346	1.55×10^{-9}	1873756:2,110,850	MAD1L1
rs10950398	7:12,264,871	6.82×10^{-9}	12233848:12,285,140	TMEM106B
rs13246482	7:109,794,839	1.51×10^{-8}	109716293:109,794,839	(No genes mapped)
rs3793577	9:23,737,627	4.73×10^{-8}	23736400:23,737,627	ELAVL2
rs7044244	9:96,397,689	1.52×10^{-8}	96349538:96,484,560	PHF2
rs10818400	9:122,664,468	1.23×10^{-8}	122655283:122,676,328	RP11-360A18.2
rs61867293	10:106,563,924	2.59×10^{-9}	106418969:106,768,514	SORCS3
rs10835766	11:31,374,329	6.35×10^{-12}	30750092:31,858,991	DCDC1; RCN1
rs644740	11:65,561,468	2.10×10^{-8}	65501060:65,566,719	OVOL1
rs1149620	11:76,506,572	1.92×10^{-9}	76464812:76,511,271	RP11-672A2.1; RP11-21L23.4
rs11608185	11:113,294,976	5.82×10^{-11}	113236199:113,451,765	DRD2
rs7305875	12:23,971,243	3.00×10^{-10}	23929026:24,077,866	SOX5
rs2193743	12:108,885,446	5.30×10^{-9}	108878314:108,888,467	RP11-13G14.4
rs73224311	12:121,344,656	3.68×10^{-8}	121068253:121,423,742	SPPL3; CLIC1P1
rs12552	13:53,625,781	1.20×10^{-18}	53605160:54,056,553	OLFM4; LINC01065; RN7SL618P; AL450423.1
rs1950829	14:42,097,937	8.10×10^{-10}	41969803:42,183,025	LRFN5
rs8037355	15:37,643,831	6.57×10^{-13}	37581276:37,840,264	RP11-597G23.1; RP11-720L8.1
rs191117454	16:1,249,053	2.06×10^{-8}	1246747:1,255,390	CACNA1H
rs1126464	16:89,704,365	3.62×10^{-10}	89669631:89,857,431	FANCA

BP, base position; Chr, chromosome.

Table II. Fine-mapping transcriptome-wide association signals in brain.

Gene	Tissue	TWAS_Z	PIP	Region
RPL31P12	brain_cerebellum	-7.61	1	1:71684831-1:74,326,484
UQCC	brain_dorsolateral_prefrontal_cortex	6.75	1	20:32813689-20:34,960,446
AXIN1	brain_cerebellar_hemisphere	-5.74	1	16:1207833-16:2,763,816
ZNF184	brain_hypothalamus	-5.13	1	6:25684587-6:26,789,628
DNAJC24	brain_dorsolateral_prefrontal_cortex	5.33	0.99	11:30141357-11:32,276,662
FAM86B3P	brain_cerebellar_hemisphere	-5.28	0.99	8:7153384-8:9,154,694
GPX1	brain_frontal_cortex_ba9	5.99	0.95	3:47727379-3:49,316,164
PRSS16	brain_cerebellum	-5.33	0.92	6:28018353-6:28,917,091
HIST1H4H	brain_dorsolateral_prefrontal_cortex	3.98	0.91	6:25684587-6:26,789,628

PIP, posterior inclusion probability; TWAS, transcriptome-wide association study.

the bidirectional causal effects between MDD and OA, indicating that the liability of depression and OA may aetiologically confer risk on one another. These complementary lines of evidence reveal novel mechanisms underlying phenotypic relationships between MDD and OA (Figure 2e).

Close links between MDD and OA have been well documented.[32] However, biological pathways mediating relationships between MDD and OA remain largely elusive. MDD and OA belong to two distinctive medical categories, therefore common genes shared between MDD and OA have rarely been systematically investigated. As yet, only a limited number of genome-wide candidate genes have been reported by GWASs and transcriptome studies on OA.[16,33–35] Our cross-trait analysis revealed 29 loci and 75 protein-coding genes shared between MDD and OA. The pleiotropic genes may at least partially mediate the cross-talk between MDD and OA in the context of disease pathogenesis.

Among the 25 protein-coding genes directly implicated by independent significant SNPs, a total of 15 genes were previously identified as genome-wide risk genes for

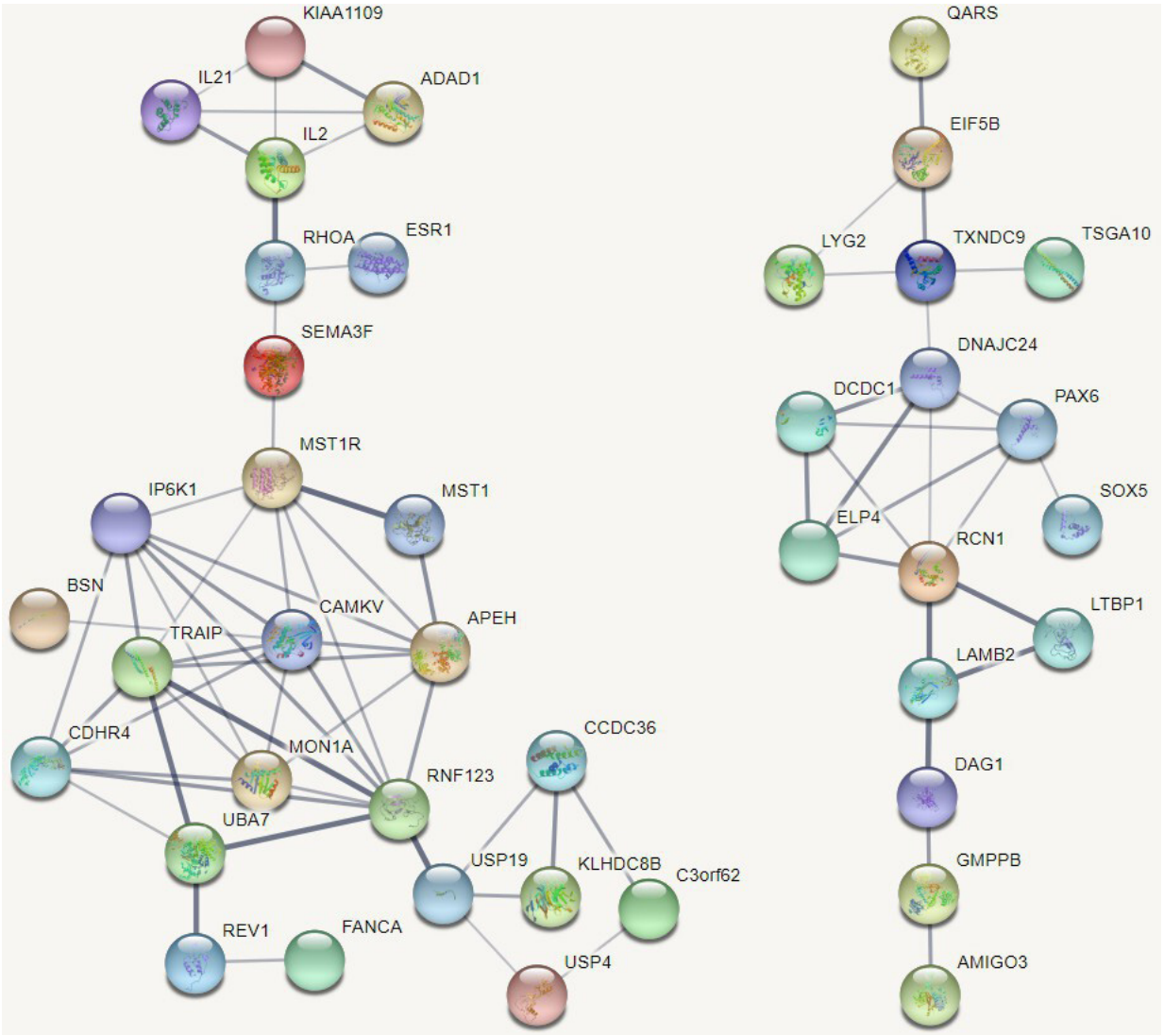

Fig. 3

Protein-protein interactions among the shared genes. These were pleiotropic protein-coding genes related to both major depressive disorder and osteoarthritis.

depression, including *DCDC1*, *DRD2*, *ELAVL2*, *KIAA1109*, *KLHDC8B*, *LRFN5*, *MAD1L1*, *NEGR1*, *OLFM4*, *PHF2*, *SORCS3*, *SOX5*, *SPPL3*, *TENM2*, and *TMEM106B*. However, the majority of the pleiotropic genes identified are novel risk genes at the genome-wide level for OA, except for two genes, *LTBP1 and RBM6*. Our study sheds new light on the genetic susceptibility of OA and MDD. Some of these genes may have implications for treatment regimens for patients comorbid with the two diseases.

Accumulating evidence indicates the involvement of oestrogen in depression.[36] Depression is associated with altered levels of neurotransmitters and abnormal functioning of the hypothalamic-pituitary-adrenal axis. Oestrogen can modulate neurotransmitter turnover to enhance the levels of serotonin and noradrenaline, and is involved in the regulation of serotonin receptor number and function.[37] Fluctuating oestrogen levels during the female reproductive life are associated with depressed mood.[38] Oestrogen exerts its biological effects chiefly through intracellular activation of oestrogen receptor α (*ESR1*) and oestrogen receptor β (*ESR2*).

ESR1 belongs to the nuclear receptor superfamily of ligand-regulated transcription factors. *ESR1* has been reported to be associated with MDD[39] and perinatal depression.[40,41] *ESR1* was implicated in anxiety-like behaviour and was identified to be a genome-wide risk gene for anxiety.[42] Associations between *ESR1* and MDD could have useful preventive and therapeutic implications, and help to lead to more personalized therapies based on one's genetic profile. Neonatal treatment with antidepressant clomipramine in rats induces changes in oestrogen receptors in different brain areas involved with the regulation of depressive-like behaviours.[43] A beneficial effect of oestrogen-containing hormone treatment (HT) has been reported in depressed peri-menopausal and postmenopausal women.[44,45]

Oestrogen and its receptors are essential for sexual development and reproductive function, but also play a role in other tissues such as bone. *ESR1* is expressed in chondrocytes, stromal cells, and osteoblasts,[46] indicating its potential role in OA. Genetic variants within *ESR1* have been reported to be associated with OA,[47,48] and were suggested to be one of the promising risk genes for OA.[6,49] *ESR1* has been repeatedly identified as a genome-wide risk gene for bone mineral density,[50–53] demonstrating its vital role in osteoporosis and fractures.[6]

The presence of oestrogen receptors in joint tissues and the increased prevalence of OA after menopause suggests the potential value of oestrogen treatment in OA patients. Oestrogen-related agents may exert an effect on subchondral bone and the surrounding tissues, including the articular cartilage, synovium, and muscle. Recent studies have suggested that oestrogen or selective oestrogen receptor modulators (SERMs) may exert a beneficial effect in OA with relative safety and tolerability profiles.[54,55] SERMs like raloxifene and bazedoxifene have been approved for the treatment of osteoporosis.[55] SERMs may be particularly beneficial for postmenopausal patients with early-stage OA or osteoporotic OA.[54,55] This cross-trait meta-analysis suggests *ESR1* as a novel genome-wide risk gene for both MDD and OA, corroborating its role in the aetiology of both OA and MDD (Figure 2d). We postulate that oestrogen or SERMs may be favourable for patients comorbid with depression and OA.

The *SOX5* gene encodes one of the SOX family of transcription factors involved in the regulation of cell fate and differentiation in neurogenesis and other discrete developmental processes.[56,57] *SOX5* haploinsufficiency leads to the neurodevelopmental disorder Lamb-Shaffer syndrome.[58] *SOX5* was a genome-wide risk gene for MDD,[15,59,60] and was associated with response to antidepressant[61] and antipsychotics.[62]

SOX5 is one member of the SOX trio (SOX5, SOX6, and SOX9) that is crucial for the development of primordial cartilage and chondrogenesis.[63,64] In addition, *SOX5* was a genome-wide gene for heel bone mineral density and may be involved in osteoporosis.[52,65,66] Our study identified *SOX5* as a novel genome-wide risk gene for OA, providing additional evidence for its involvement in OA. However, further studies are warranted to elucidate the mechanisms of *SOX5* in the pathogenesis of MDD.

Empirical evidence has shown that *SOX5* was associated with response to statin.[67] Statins are used widely in primary and secondary prevention of cardiovascular disease due to their cholesterol-lowering properties. Statin has been reported to have beneficial effects on OA,[68] especially knee OA.[69,70] Statin use is associated with decreased risks of osteoporosis, hip fracture, and vertebral fracture in stroke patients.[71] A meta-analysis indicated that statin treatment may be associated with a decreased risk of overall fractures and hip fractures, and increased bone mineral density and osteocalcin.[72]

Statins also have anti-inflammatory effects independent of their lipid-lowering mechanisms. Low-grade inflammation is repeatedly observed in depression patients, and anti-inflammatory drugs have shown antidepressant actions. Studies have suggested that statin use is associated with a reduced risk of MDD,[73] which may be explained by the anti-inflammatory properties of statin.[74] It was reported that concomitant treatment with SSRIs and statins leads to better response compared with SSRIs alone.[75,76] It is suggested that statins used in combination with psychotropic medications may be effective for various psychiatric conditions, including depression, schizophrenia, and dementia.[77] Antidepressants have also been used in OA patients. A meta-analysis indicated that duloxetine has moderate benefits on pain, function, and quality of life in knee OA patients.[78] Therefore, it is tempting to speculate that statins may be more effective to be used as an add-on treatment to an antidepressant for patients with comorbid depression and OA/osteoporosis (Figure 2d).

To identify potentially causal genes involved in MDD and OA, we used the fine-mapping of TWAS hits to estimate the causality in the brain tissue. A total of 80 genes were in the 90%-credible set, including nine genes with high PIP. Three of the nine genes are shared by MDD and OA in our meta-analysis, including *RPL31P12*, *DNAJC24*, and *GPX1*. The *RPL31P12* gene, located in 1p31.1, is a pseudogene with unknown functions. The *DNAJC24* gene maps to 11p13, and its function is not fully understood. It has been reported that silencing of *DNAJC24* gene transcription is associated with immunotoxin resistance.[79]

GPX1 in the 3p21.31 region was included in the credible gene set with a PIP of 0.95 in the left ventricle of the heart (Figure 1c). *GPX1* encodes a selenium-containing protein that catalyzes the reduction of organic hydroperoxides and hydrogen peroxide by glutathione, and protects cells against oxidative damage. Previous studies indicated that antioxidant disturbances play a vital role in the pathogenesis of neurodegenerative disorders, including depression.[80] Expression levels of *GPX1* were lower in oligodendrocytes from MDD donors as compared to control donors, which may account for shortened telomere length in these patients.[81] Decreased levels of *GPX1* were associated with depression severity in the patients.[82] Animal studies showed that the expression of *GPX1* in the brain changed following chronic mild stress or venlafaxine exposure.[83] A previous GWAS has implicated *GPX1* in depression.[59]

The phenotypes of OA consist of disturbance of cartilage extracellular matrix (ECM) metabolism and the imbalance of cartilage homeostasis resulting from pro-inflammatory factors and oxidative stress. GPX1 is a major antioxidant enzyme in osteoclasts and is highly expressed in chondrocytes.[84] GPX1 plays a role in chondrocyte differentiation and cartilage formation.[85] It was reported that *GPX1* messenger RNA (mRNA) expression was lower in damaged cartilage than in smooth cartilage from the OA patients.[86] It was reported that bone marrow-derived stem cell-treated ataxic mice showed higher levels of catalase and GPX1.[87] Oestrogen is a vital regulator in

maintaining bone health, and *GPX1* is upregulated by oestrogen.[88] Therefore, our study links the cross-talk between *GPX1* and oestrogen to the pathogenesis of both depression and OA (Figure 2d).

Shared genetic liability between MDD and OA offers the potential to evaluate osteoarthritic risk in MDD patients and to evaluate the risk to develop depression in OA patients, using strategies like polygenic risk scores. Identification of shared genetic basis between MDD and OA may guide drug discovery, and inform early prediction and personalized treatment for the comorbidities. Since medical comorbidities contribute to poor treatment effects, we argue that it may be beneficial to incorporate screening of depression into the treatment regimen for OA, since improved management may be achieved with add-on psychological or psychiatric interventions for subgroups with higher depression.

The presented study has several strengths. First, we typically prioritized the largest available datasets as a study backbone. Furthermore, to avoid potential population heterogeneity across the studies, we limited our analysis to individuals of European ancestry. Lastly, we employed multiple analytic frameworks to systematically elucidate the genetic relationships between MDD and OA.

However, several limitations should be noted. As our analysis was limited to a genetic component of each trait, the presented results should be interpreted cautiously, with the understanding that human traits result from a complex web of interactions among a plethora of psychosocial-environmental factors. We could not exclude the possibility that some patients with OA may have comorbid depression, which may bias the result. TWAS associations may potentially contain noises, since the gene expression levels were imputed from weighted linear combinations of SNPs. Due to the lack of an eQTL reference dataset in bone and joints, the causality of genes could not be evaluated using TWAS signals for OA.

In summary, our findings indicated that MDD and OA share substantial genetic liability, which may also confer risk on one another. Our study reveals novel mechanisms underlying phenotypic relationships between MDD and OA.

Supplementary material

Tables showing loci and genes identified by the meta-analysis result, gene-trait associations identified in previous studies, and transcriptome-wide association study results; figure showing quantile-quantile plot of the meta-analysis.

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