Research Square

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A Proteome-Wide Association Study Identified Candidate Human Brain Proteins Associated with Coffee Consumption

Chun'e Li
Xi'an Jiaotong University
Xiao Liang
Xi'an Jiaotong University
Yumeng Jia
Xi'an Jiaotong University
Yan Wen
Xi'an Jiaotong University
Huijie Zhang
Xi'an Jiaotong University
Shiqiang Cheng
Xi'an Jiaotong University
Chuyu Pan
Xi'an Jiaotong University
Jingxi Zhang
Xi'an Jiaotong University
Zhen Zhang
Xi'an Jiaotong University
Yujing Chen
Xi'an Jiaotong University
Xuena Yang
Xi'an Jiaotong University
Peilin Meng
Xi'an Jiaotong University
Yao Yao
Xi'an Jiaotong University
Feng Zhang (fzhxjtu@mail.xjtu.edu.cn)
Xi'an Jiaotong University
Cuiyan Wu
Xi'an Jiaotong University
Sen Wang

Xi'an Jiaotong University

Yujie Ning

Xi'an Jiaotong University

Xi Wang

Xi'an Jiaotong University

Research

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Abstract

Background

Increasing evidence suggests the association between caffeine and the brain and nervous system. However, there is limited research on the genetic associations between coffee consumption subtypes and brain proteome, plasma proteomes, and peripheral metabolites.

Methods

First, proteome-wide association study (PWAS) of coffee consumption subtypes was performed by integrating two independent genome-wide association study (GWAS) datasets (91,462–502,650 subjects) with two reference human brain proteomes (ROS/MAP and Banner), by using the FUSION pipeline. Second, transcriptome-wide association study (TWAS) analysis of coffee consumption subtypes was conducted by integrating the two gene expression weight references (RNAseq and splicing) of brain RNA-seq and the two GWAS datasets (91,462–502,650 subjects) of coffee consumption subtypes. Finally, we used the LD Score Regression (LDSC) analysis to evaluate the genetic correlations of coffee consumption subtypes with plasma proteomes and peripheral metabolites.

Results

For the traits related to coffee consumption, we identified 3 common PWAS proteins, such as *MADD* ($P_{PWAS-Banner-dis}$=0.0114, $P_{PWAS-ROS/MAP-rep}$ =0.0489). In addition, 11 common TWAS genes were found in two cohorts, such as *ARPC2* ($P_{TWAS-splicing-dis}$ =2063×10^{-12}, $P_{TWAS-splicing-dis}$ =1.25×10^{-10}, $P_{TWAS-splicing-dis}$ =1.24e-08, $P_{TWAS-splicing-rep}$ =3.25×10^{-9} and $P_{TWAS-splicing-rep}$ =3.42×10^{-13}). Importantly, we have identified 8 common genes between PWAS and TWAS, such as *ALDH2* ($P_{PWAS-banner-rep}$ =1.22×10^{-22}, $P_{TWAS-splicing-dis}$ = 4.54×10^{-92}). For the LDSC analysis of human plasma proteome, we identified 11 plasma proteins, such as *CHL1* (P_{dis} = 0.0151, P_{rep} =0.0438). For the LDSC analysis of blood metabolites, 5 metabolites have been found, such as *myo-inositol* (P_{dis} = 0.0073, P_{dis} = 0.0152, P_{dis} =0.0414, P_{rep} =0.0216).

Conclusions

We identified several brain proteins and genes associated with coffee consumption subtypes. In addition, we also detected several candidate plasma proteins and metabolites related to these subtypes.

Introduction

Coffee is the second most commonly consumed beverage worldwide after water and is the main source of caffeine(1). Caffeine is a mild central nervous system stimulant, and it has a wide range of mental effects (2, 3), including improving mental alertness, speeding up information processing, making people awake, and delaying the need for sleep (3, 4). However, there are still many controversies regarding the benefits and risks of caffee to human health (5).

Besides caffeine, coffee also contains a lot of plant-active ingredients, such as chlorogenic acid (*3–3,4-Dihydroxycinnamoyl quinic acid*), caffeic acid (*3,4-Dihydroconnamic acid*), hydroxyhydroquinone (*1,2,4-Trihydroxybenzene*) and so on.(6) These ingredients are effective antioxidants, which can protect the body from the harmful effects of free radicals and have significant benefits on human health (5, 7). However, multiple studies have shown that coffee consumption increases the risk of cancer (8), blood pressure (9, 10), and myocardial infarction (11). Furthermore, chronic coffee consumption can lead to caffeine dependence (12). Most people experience caffeine withdrawal symptoms after stopping caffeine intake, such as headaches, drowsiness, and fatigue, although these symptoms generally do not last long (1, 13, 14).The paradox about the benefits and risks of coffee may be due to differences in coffee consumption, as previous studies have shown that estimates of heritability for coffee consumption range from 0.39 to 0.56 (3, 15).

In recent years, most previous studies on coffee consumption have focused on genetic polymorphisms (11, 16, 17). Although caffeine has a significant effect on the brain, neuronal network, and nervous system (18, 19), the research about the relationship between brain protein and coffee consumption is limited, and only a few literature have reported that caffeine could reduce the level of brain beta-amyloid (20). Previous studies have reported that caffeine acts as an antagonist of adenosine A1 and A2A receptors in the brain, which can cause excessive excitement of the central nervous system (21, 22), and Ricardo Magalhães et al. indicated that large amounts of coffee and caffeinated products could affect the functional connection of the brain at rest, thereby affecting mood, alertness, and preparation for action (18). Therefore, identifying the brain proteins associated with coffee have great significance.

Although we have known that coffee consumption is a modifiable risk factor for chronic diseases, epidemiological studies do not always support associations between specific foods or nutrients and disease endpoints (23). Metabolomics, as an effective approach for discovering the biomarkers of dietary intake, can measure metabolites in biological fluids and may accurately reflect the relationship between dietary intake and disease risk (24). In addition, the development of proteomics is also driving research in the field of coffee (25), using a highly sensitive and specific proteomics analysis can identify coffee consumption-induced changes. However, only limited information identified human blood metabolites and human plasma proteome related to coffee consumption (26–28). No studies have studied the genetic correlations between coffee and blood metabolites and plasma proteome.

Genome-wide association study (GWAS) has been widely used in various genetic studies (29, 30), but there are some limitations in the use of GWAS (31, 32). Proteome-wide Association Study (PWAS) is a new method for detecting gene-phenotype associations mediated by changes in protein function. PWAS

can reduce the burden of multiple test corrections and provide specific functional explanations for the discovered protein-coding genes (33). Transcriptome-wide Association Study (TWAS) integrates GWAS and gene expression datasets, in order to identify genetic trait associations (34). In addition, considering that causality between gene expression and the trait cannot be guaranteed, TWAS can prioritize candidate causal genes and tissues underlying GWAS loci (34).

In the present study, we performed PWAS and TWAS to identify the new genes associated with coffee consumption subtypes (35, 36). In addition, we used linkage disequilibrium score regression (LDSC) to compute heritability and genetic correlation (37, 38), and analyze the plasma proteomes and blood metabolites related to coffee addiction and coffee metabolism.

Results

PWAS results of coffee consumption subtypes

For the discovery and replication cohorts of PWAS, 3 overlapping proteins were identified based on the ROS/MAP and Banner human brain proteomes, including *C14orf159*, *AOC2* and *MADD*. *C14orf159* gene was detected for coffee consumed ($P_{PWAS-Banner-dis}$=0.0126), instant coffee intake ($P_{PWAS-ROS/MAP-dis}$ =0.0052), added milk to instant coffee ($P_{PWAS-ROS/MAP-dis}$ =0.0095), and coffee consumption among drinkers ($P_{PWAS-ROS/MAP-rep}$= 0.0306, $P_{PWAS-Banner-rep}$= 0.0254). Furthermore, the *AOC2* was identified in the coffee type: Decaffeinated coffee (any type) ($P_{PWAS-ROS/MAP-dis}$ =0.0074) and extreme coffee trait ($P_{PWAS-ROS/MAP-rep}$ =0.0097). *MADD* gene was found in the coffee type: Instant coffee ($P_{PWAS-Banner-dis}$=0.0114) and coffee consumption among drinkers ($P_{PWAS-ROS/MAP-rep}$ =0.0489). The detailed results are shown in Table 1.

Table 1
Common proteins of PWAS in the discovery and replication cohort of coffee consumption-related traits.

Gene	Discovery cohort			Replication cohort		
	PWAS P	PWAS Z	Trait	PWAS P	PWAS Z	Trait
C14orf159	0.0126**	2.2872	Coffee consumed	0.0254**	2.1746	Coffee consumption among drinkers
	0.0052*	2.1218	Instant coffee intake	0.0306*	2.1703	
	0.0095*	2.0500	Added milk to instant coffee			Coffee consumption among drinkers
AOC2	0.0074*	-2.1787	Coffee type 1	0.0097*	-2.3710	extreme coffee trait
MADD	0.0114**	-2.3824	Coffee type 2	0.0489*	2.3616	Coffee consumption among drinkers
Note:						
* Reference human brain proteome of ROS/MAP.						
** Reference human brain proteome of Banner.						
Coffee type 1: Coffee type: Decaffeinated coffee (any type).						
Coffee type 2: Coffee type: Instant coffee.						
extreme coffee trait: extreme coffee trait: heavy ('case') vs no/low ('control') regular coffee consumption.						

TWAS results of coffee consumption subtypes

A total of 11 common genes were found in the discovery and replication cohort based on the rnaseq and splicing RNA expression weights, such as,DMXL1 UBE3B, ARPC2, LRRC37B and LAMA1. DMXL1 was found in the coffee intake ($P_{TWAS\text{-splicing-dis}}$=0.0008) and extreme coffee trait ($P_{TWAS\text{-splicing-rep}}$=0.0028). UBE3B was detected in coffee intake ($P_{TWAS\text{-splicing-dis}}$=0.0004) and coffee consumption among drinkers ($P_{TWAS\text{-splicing-rep}}$=0.0009). ARPC2 was identified in the coffee intake ($P_{TWAS\text{-splicing-dis}}$ =2.63×10^{-12}), coffee consumed ($P_{TWAS\text{-splicing-dis}}$ =1.25×10^{-10}), intake of sugar added to coffee ($P_{TWAS\text{-splicing-dis}}$ =1.24e-08), the extreme coffee trait ($P_{TWAS\text{-splicing-rep}}$ =3.25×10^{-9}) and coffee consumption among drinkers ($P_{TWAS\text{-splicing-rep}}$ =3.42×10^{-13}). LRRC37B was found in the instant coffee intake ($P_{TWAS\text{-splicing-dis}}$ =0.0013) and extreme coffee trait ($P_{TWAS\text{-splicing-rep}}$ =0.0010). LAMA1 was discovered in the added milk to instant coffee ($P_{TWAS\text{-rnaseq-dis}}$=0.0033) and coffee consumption among drinkers ($P_{TWAS\text{-rnaseq-rep}}$=0.0053). Additional genes and more details are shown in Table 2.

Table 2
Common genes of TWAS in discovery and replication cohort of coffee consumption-related traits.

Gene	Discovery cohort			Replication cohort		
	TWAS P	TWAS Z	Phenotype	TWAS P	TWAS Z	Phenotype
DTX2P1-UPK3BP1-PMS2P11	0.0024†	3.3864	Coffee intake	0.0003† 0.0004†	4.4028 3.4505	Coffee consumption among drinkers extreme coffee trait
DMXL1	0.0008‡	3.1053	Coffee intake	0.0028‡	3.4063	extreme coffee trait
UBE3B	0.0004‡	-4.3926	Coffee intake	0.0009‡	-3.4096	Coffee consumption among drinkers
ARPC2	2.63×10^{-12}‡ 1.25×10^{-10}‡ 1.24×10^{-08}‡	-2.8947 2.0657 2.3527	Coffee intake Coffee consumed Intake of sugar added to coffee	3.25×10^{-09}‡ 3.42×10^{-13}‡	-2.4636 -2.3679	extreme coffee trait Coffee consumption among drinkers
LRRC37B	0.0013‡	2.8208	Instant coffee intake	0.0010‡	-3.0155	extreme coffee trait
LAMA1	0.0033†	-2.9907	Added milk to instant coffee	0.0053†	-3.4400	Coffee consumption among drinkers

Note:

† RNA expression weight of rnaseq.

‡ RNA expression weight of splicing.

Coffee type 1: Coffee type: Decaffeinated coffee (any type).

Coffee type 2: Coffee type: Instant coffee.

extreme coffee trait: extreme coffee trait: heavy ('case') vs no/low ('control') regular coffee consumption.

Gene	Discovery cohort			Replication cohort		
	TWAS P	TWAS Z	Phenotype	TWAS P	TWAS Z	Phenotype
CDH10	0.0043‡ 0.0032‡	-3.1099 -3.0835	Filtered coffee intake Added milk to filtered coffee	0.0020†	3.4620	Coffee consumption among drinkers
EXOC4	0.0142‡	2.6800	Intake of sugar added to coffee	0.0238‡	3.2750	Coffee consumption among drinkers
KRIT1	3.13×10⁻⁰⁶† 6.08×10⁻¹³‡	-2.2945 -2.5255	Coffee type 1 Coffee type 1	7.96×10⁻³¹‡	-3.0784	extreme coffee trait
AKAP9	1.79×10⁻⁰⁷‡	-2.2877	Coffee type 1	2.33×10⁻²²‡	-3.0909	extreme coffee trait
STYXL1	0.0037‡	4.1899	Coffee type 2	0.0033‡	7.6709	Coffee consumption among drinkers
Note:						
† RNA expression weight of rnaseq.						
‡ RNA expression weight of splicing.						
Coffee type 1: Coffee type: Decaffeinated coffee (any type).						
Coffee type 2: Coffee type: Instant coffee.						
extreme coffee trait: extreme coffee trait: heavy ('case') vs no/low ('control') regular coffee consumption.						

Common genes shared by PWAS and TWAS

8 common genes have been found in both PWAS and TWAS, as shown following, ALDH2 ($P_{PWAS-banner-rep}$ =1.22×10^{-22} for coffee consumption among drinkers, $P_{TWAS-splicing-dis}$ = 4.54×10^{-92} for filtered coffee intake), ALKBH7($P_{PWAS-ROS/MAP-dis}$ =0.0078 for instant coffee intake, $P_{PWAS-ROS/MAP-dis}$ =0.0055 for intake of sugar added to coffee, $P_{TWAS-splicing-dis}$ =0.0017 for instant coffee intake), NME1 ($P_{PWAS-Banner-dis}$ =0.0173 for coffee consumed, $P_{TWAS-rnaseq-dis}$ =0.0172 for coffee consumed, $P_{TWAS-rnaseq-dis}$ =0.0120 for added milk to instant coffee), and SNUPN

($P_{PWAS-ROS/MAP-dis}$=0.0113 for coffee consumed, $P_{PWAS-ROS/MAP-dis}$=0.0212 for instant coffee intake, $P_{PWAS-ROS/MAP-dis}$ =0.0036 for added milk to instant coffee, $P_{TWAS-splicing-dis}$ =0.0454, $P_{TWAS-splicing-dis}$ =0.0456 for instant coffee intake, $P_{TWAS-splicing-dis}$ =0.0144, $P_{TWAS-splicing-dis}$ =0.0147 for added milk to instant coffee). Additional findings and more details are shown in Table 3.

Table 3
Common results for both PWAS and TWAS.

Gene	PWAS			TWAS		
	P	Z	Phenotype	P	Z	Phenotype
ALDH2	1.22×10^{-22}**	-2.2619	Coffee consumption among drinkers [b]	4.54×10^{-92}‡	2.0545	Filtered coffee intake [a]
ALKBH7	0.0078*	-3.2836	Instant coffee intake [a]	0.0017‡	3.2776	Instant coffee intake [a]
	0.0055*	-2.1135	Intake of sugar added to coffee [a]			
NME1	0.0173**	-2.1701	Coffee consumed [a]	0.0172†	-2.1701	Coffee consumed [a]
				0.0120†	-2.1884	Added milk to instant coffee [a]
RABEP1	0.0213**	-3.6284	Coffee type 3[a]	0.0019†	3.1991	Coffee intake [a]
SNUPN	0.0113*	-2.7508	Coffee consumed [a]	0.0454‡	3.4531	Instant coffee intake [a]
	0.0212*	-3.4531	Instant coffee intake [a]	0.0456‡	3.4531	
	0.0036*	-2.5991	Added milk to instant coffee [a]	0.0144‡	2.5991	Instant coffee intake [a]
				0.0147‡	2.5991	Added milk to instant coffee [a]
						Added milk to instant coffee [a]
THG1L	0.0064*	-3.0711	Coffee type 3 [a]	0.0018†	-2.7946	Coffee type 3 [a]
TMED5	4.72×10^{-10}*	3.3872	Decaffeinated coffee [a]	1.54×10^{-29}‡	-4.4548	Coffee type 1 [a]
				0.0208‡	-3.1598	Coffee type 3 [a]

Gene	PWAS			TWAS		
	P	Z	Phenotype	P	Z	Phenotype
XRCC6BP1	0.0166*	-3.5510	Coffee consumption among drinkers(rep) [a]	0.0108†	-3.5510	Coffee consumption among drinkers [b]
Note:						
* Reference human brain proteome of ROS/MAP.						
** Reference human brain proteome of Banner.						
† RNA expression weight of rnaseq.						
‡ RNA expression weight of splicing.						
a: The discovery cohort.						
b: The replication cohort.						
Coffee type 1: Coffee type: Decaffeinated coffee (any type).						
Coffee type 3: Coffee type: Ground coffee (include espresso, filter etc).						

LDSC regression analyses between coffee consumption subtypes and plasma proteins

We found 93 plasma proteins and 36 plasma proteins associated with coffee consumption-related traits in discovery cohort and replication cohort (Supplement Table 2, 3). A total of 11 overlapping plasma proteins (*CHL1, CO1A1, F177A, LTBP4, MYOM2, MYPC1, P5I11, PLOD3, RN148, SAP, SIA7F*) have been identified in discovery and replication cohort. Among those, CHL1 was discovered in the added milk to filtered coffee (rg $_{dis}$ = 0.8030, P_{dis} = 0.0151) and the coffee consumption among drinkers (rg $_{rep}$ = 0.5043, P_{rep} =0.0438). PLOD3 was identified in the coffee type: Instant coffee (rg $_{dis}$ = -0.3291, P_{dis} = 0.0435) and in the extreme coffee trait (rg $_{rep}$ = -0.5846, P_{rep} = 0.0334). MYPC1 was found in the coffee type: Decaffeinated coffee (any type) (rg $_{dis}$ = 0.5096, P $_{dis}$ = 0.0098), coffee type: Instant coffee (rg $_{dis}$ = -0.3964, P $_{dis}$ = 0.0018), coffee consumption among drinkers (rg $_{rep}$ = 0.4286, P $_{rep}$ = 0.0277), and extreme coffee trait (rg $_{rep}$ = 0.3904, P $_{rep}$ = 0.0401). The detailed information is presented in Supplementary table 6 and Fig. 1.

LDSC regression analyses between coffee consumption subtypes and blood metabolites

For the genetic associations between blood metabolites and coffee consumption-related traits, a total of 102 genetic associations were found in the discovery cohort and 7 genetic associations were found in the replication cohort (Supplement Table 4,5). 5 blood metabolites were both identified in the discovery and replication cohorts, such as n-Butyl Oleate, myo-inositol, X-11423, 1-arachidonoylglycerophosphoinositol*, 1-palmitoylglycerophosphoethanolamine. n-Butyl Oleate was identified in coffee consumed (rg_{dis} = -0.4626, P_{dis} = 0.0370), and coffee consumption among drinkers (rg_{rep} = 0.3534, $P r_{ep}$ = 0.0170). myo-inositol was detected for coffee type: Instant coffee (rg_{dis} = -0.1620, P_{dis} = 0.0073), coffee type: Ground coffee (include espresso, filter etc) (rg_{dis} = 0.1208, P_{dis} = 0.0152), intake of sugar added to coffee (rg_{dis} = -0.2177, P_{dis} =0.0414) and coffee consumption among drinkers (rg_{rep} = -0.2238, P_{rep} =0.0216). The detailed information is presented in Supplementary table 7 and Fig. 2.

Table 4
Diseases associated with coffee consumption and significant genes/proteins.

Related diseases	Genes/Proteins
Breast cancer	ALDH2, ARPC2, MADD, CDH10, AKAP9,LAMA1 NME1, EXOC4, RABEP1
Gastric Cancer	ALDH2, ARPC2, C14orf159, AKAP9,NME1
Alzheimer's Disease	ALDH2, MADD, AKAP9,LAMA1
Colorectal Cancer	ALDH2,AKAP9, CDH10
Intellectual disability	LAMA1, STYXL1, UBE3B
Melanoma	NME1, SNUPN
Lung cancer	CDH10,AKAP9
Cardiovascular Disease	ALDH2, EXOC4

Discussion

In this study, we sought to identify brain proteins associated with coffee consumption subtypes by PWAS and TWAS. Our study focused on the overlapping PWAS and overlapping TWAS genes in discovery and replication cohort, as well as genes that were shared by PWAS and TWAS. Subsequently, LDSC was used to demonstrate the genetic association and overlapping genetic architecture between coffee consumption subtypes and plasma proteins and peripheral metabolites.

For all the results of PWAS and TWAS, we found some meaningful genes. The first gene to note is *ALDH2*. Among the genetic variants encoding several alcohol-metabolizing enzymes, the alcohol dehydrogenase (*ADH*) and aldehyde dehydrogenase (*ALDH*) are two of the most genetically related to the risk of alcohol dependence (39). Among them, *ALDH2* is known for its restriction of alcohol consumption and protection of alcoholism, and mutations and impaired enzyme activity of *ALDH2* will lead to the accumulation of acetaldehyde (40). The point is similar to the GO terms of *ALDH2* shown in GCBI:

GO:0006066 ~ alcohol metabolic process, GO:0006068 ~ *ethanol catabolic process*. *ALDH2* dysfunction has been confirmed to be involved in a wide range of human diseases, such as breast cancer, gastric cancer, colorectal cancer, Alzheimer's disease, and cardiovascular disease (41–43). Of note, these diseases have evidence that they are related to coffee consumption (44, 45). In summary, we have sufficient evidence to show that ALDH2 is related to coffee consumption to a certain extent. Similarly, for the *ARPC2*, we also found some related GO terms from GCBI, such as *GO:0034314 ~ Arp2/3 complex-mediated actin nucleation*, *GO:0070358 ~ actin polymerization-dependent cell motility* and so on. Previous studies have also confirmed that these functions affect alcohol dependence and alcohol consumption through various biological pathways. (46, 47). Specially, from GCBI, we found *UBE3B* related GO terms, including *GO:0006511 ~ ubiquitin-dependent protein catabolic process* and *GO:0000209 ~ protein polyubiquitination*. From previous researches, we can find that the ubiquitination system may play a major role in the biology of synaptic plasticity (48, 49), and the density of *UBE3B* immunoreactive pyramidal neurons is decreased in schizophrenia subjects (50). In other words, *UBE3B* is associate with the human brain's nervous system. We're still trying to figure out whether the *UBE3B* relationship with the human brain's nervous system affects coffee consumption.

To determine the relationship between the findings of our study and coffee consumption subtypes, we explore the related diseases of the results in our study and summarized the top 8 diseases by using GCBI and searching literature (Table 4). In these diseases, a total of 9 genes are associated with breast cancer, such as *ARPC2*, *ALDH2* and *MADD*. For example, ZHONGLE et al. have reported that *ARPC2* promotes proliferation and metastasis of breast cancer (51), and the relationship between coffee consumption and breast cancer has also been confirmed, the study of Cristina et al. mentioned that drinking coffee is negatively associated with the risk of breast cancer in postmenopausal women (52). In addition, in our study, there are 5 genes related to gastric cancer, including *ALDH2*, *ARPC2*, *C14orf159* and so on. *ALDH2* polymorphism changes the risk of gastric cancer (53), and *ARPC2* plays an analgesic effect in gastric cancer, providing a new target for gastric cancer treatment (54). It is worth noting that the relationship between gastric cancer and coffee consumption has also been confirmed, and coffee may have a potentially beneficial effect on the incidence and mortality of gastric cancer (55). Moreover, our findings are also related to Alzheimer's disease, colorectal cancer, intellectual disability, melanoma, lung cancer, cardiovascular disease. Interestingly, there is evidence that these diseases are related to coffee consumption (5, 55).

In addition, a total of 11 common plasma proteins are significantly genetically related to coffee consumption subtypes both in discovery and replication cohorts, including Neural cell adhesion molecular L1-like protein (*CHL1*), Procollagen-lysine,2-oxoglutarate 5-dioxygenase 3 (*PLOD3*) and so on. Among those proteins, *CHL1*was associated with the development and progression of tumors more than once (56, 57). which is consistent with our study result. In addition, GCBI also suggests that *CHL1* is associated with schizophrenia, depression, and a previous study suggested that coffee and caffeine consumption were significantly associated with decreased risk of depression (58).

5 overlapping blood metabolites (*n-Butyl Oleate*, *myo-inositol*, *X-11423*, *1-arachidonoylglycerophosphoinositol**, *1-palmitoylglycerophosphoethanolamine*) were associated with the coffee consumption-related traits both in the discovery and replication cohort. *Myo-inositol* (MI) has been widely studied as an insulin sensitizing factor. It has the functions of increasing insulin sensitivity, reducing hyperandrogenism, and improving the menstrual cycle (59). Therefore, it is often used to treat and improve polycystic ovary syndrome (PCOS) and gestational diabetes mellitus (GDM) (59, 60).

On the whole, our study has several strengths. Firstly, this study was conducted in two independent GWAS datasets, increasing the credibility of the study. Secondly, most previous studies only used PWAS for analysis. In this study, PWAS and TWAS were carried out simultaneously, and the results of TWAS were used to verify the results of PWAS. Third, for PWAS analysis, we combined two reference human proteomes with two independent GWAS datasets to increase the accuracy of the study results. Similarly, for TWAS analysis, we also integrate two RNA expression weights with two independent GWAS datasets. Finally, we analyzed the genetic correlation between coffee consumption subtypes and human blood metabolites and human plasma proteomes from the perspectives of metabolomics and proteomics, which has never been reported in previous studies.

Nonetheless, there are two limitations of this study that should be noted. First, the GWAS datasets were all from European samples, and although large samples have been included, we need to be cautious about the promotion of research results in other ethnic groups. Second, although we used two reference human brain proteomes in both discovery and replication cohorts at the same time, this study still is limited by the number of reference brain proteomes($N_{ROS/MAP}$=376, N_{Banner}=152). Larger reference human brain proteomes are needed to alleviate this issue.

Conclusions

In summary, our study determined that a series of genes may participate in coffee metabolism and addiction by regulating its brain protein abundance. These candidate genes may be potential targets for future research on the mechanism of coffee addiction. In addition, we also found a genetic correlation between coffee consumption-related phenotypes and protein and metabolites. This provides clues for the subsequent metabolomics and proteomics analysis of coffee consumption.

Materials And Methods

GWAS dataset1 of coffee consumption

GWAS dataset1 (N = 502,650), the discovery cohort, was downloaded from the Neale Lab (https://nealelab.github.io/UKBB_ldsc/downloads.html*)*, which was performed association analyses for over 2000 phenotypes from the UK Biobank. The UK Biobank (http://www.ukbiobank.ac.uk*)* is a large-scale biomedical database and research resource, containing health information, hospital record, and genetic data for 502,656 participants aged 40 to 69 from 2006 to 2010. All participants agreed to use

their anonymous data and samples for any health-related research. Our research has been approved by the UK Biobank. A total of 12 coffee consumption subtypes were contained in the discovery cohort, including coffee intake, coffee type: Decaffeinated coffee (any type), coffee type: instant coffee, coffee type: Ground coffee (include espresso, filter etc), coffee type: Other types of coffee, coffee consumed, instant coffee intake, added milk to instant coffee, filtered coffee intake, added milk to filtered coffee, decaffeinated coffee and intake of sugar added to coffee. the annotations for each trait can be found in Supplementary Table 1.

GWAS dataset2 of coffee consumption

GWAS dataset2 (N = 91,462), the replication cohort, was downloaded from the DigitalHub, (https://digitalhub.northwestern.edu/collections/afec3d3f-5ee6-468a-b8b4-80ab6d0402ac*)* (36). This study includes the population of European, African American, and Indian ancestry. All phenotypic data were previously collected through interviews or self-questionnaires. Among coffee consumers, the primary phenotype was that the daily consumption of coffee is dominated by regular coffee. Coffee data collected categorically (for example, 2–3 cups per day) were converted to cups per day by taking the median value of each category (for example, 2.5 cups per day). The secondary phenotype was the comparison of high with infrequent/non-coffee consumers. More details of study design, participant characteristics, genotyping and imputation can be found in the published study(36). A total of 2 traits were contained in the replication cohort, including coffee consumption among drinkers and extreme coffee trait: heavy ('case') vs no/low ('control') regular coffee consumption. The annotations for each phenotype can be found in Supplementary Table 1.

PWAS Analyses

We performed the PWAS analysis by integrating the GWAS of coffee consumption summary datasets and human brain proteomes by FUSION pipeline (http://gusevlab.org/projects/fusion/*)* to determine the brain proteins associated with coffee consumption. Firstly, in both discovery and replication cohorts, we used two references human brain proteomes, one of the references human brain proteomes were generated from the dorsolateral prefrontal cortex (dPFC) of postmortem brain samples donated by 400 ROS/MAP participants of European ancestry (61). Participants of ROS/MAP provided informed consent and signed the "Anatomy Gift Act", their data and biological specimens were allowed to be used for future studies, the ROS/MAP studies were approved by the Institutional Review Board of Rush University Medical Center 376 individuals with both proteomic and genetic data were included in the analyses after quality control (62). another references human brain proteome was profiled from dPFC of postmortem brain samples donated by 198 European participants of the Banner Sun Health Research Institute (Banner). Similarly, after quality control, 152 individuals with both proteomic and genetic data were included in the analyses (62).

TWAS Analyses

The TWAS of coffee consumption was performed by the FUSION software (http://gusevlab.org/projects/fusion/*)* (63). Firstly, the prediction model of FUSION was used to calculate

the gene expression weight, then, the expression weights were combined with the GWAS summary dataset to compute the association statistics between gene expression levels and target diseases. The Bayesian sparse linear mixed model (BSLMM) was used to compute the SNP expression weights of the 1-Mb cis loci of the given gene(64). In this analysis, linkage disequilibrium (LD) between SNPs was considered and the input gene expression data was treated as a genotype linear model with weights. The gene expression weight reference data of brain RNA-seq was derived from the dorsolateral prefrontal cortex of 452 European individuals collected by the Common Mind Consortium (CMC)(65).

LDSC Analyses

The human plasma proteomes were derived from a published study (66), which identified 1,927 genetic associations with 1,478 proteins, including trans associations for 1,104 proteins. In addition, the human blood metabolites also come from a previous study(67), which included 7,824 adults from two European population studies. Researchers ultimately reported genome-wide significant associations of 145 metabolic sites in human blood and biochemical connectivity with more than 400 metabolites in human blood. The LDSC software (v1.0.0; https://github.com/bulik/ldsc*)* was used to estimate the genetic correlation of coffee consumption with plasma proteome and blood metabolites, based on the GWAS summary datasets (68). The principle of LDSC based on the fact that genetic variants labeling more genomes (for example, with high LD scores) are more likely to label causal variants, so the average statistics are higher than genetic variants with low LD scores. Briefly, LDSC provides a way to determine whether a trait-trait correlation (as opposed to a SNP-trait correlation) is due to the presence of confounding factors that affect the two traits. The European LD scores, computed from the 1,000 Genomes by the developers, were used in this study (69).

Gene-Cloud of Biotechnology Information (GCBI)

Gene-Cloud of Biotechnology Information (GCBI, https://www.gcbi.com.cn*)* (70) is a platform that combines various sample information, genetic information, research results, data algorithms, and bioinformatics, which generate a genetic knowledge base, covering biology, mathematics, informatics, medicine, computer science, graphics, and other disciplines. The GCBI platform includes more than 120 million genome samples, approximately 90,000 tumor samples, and more than 17 million genetic information. In this study, we used GCBI to explore the significant genes associated with diseases, regulatory networks, and predict transcription factors.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Chun'e Li contributes to the design of the work, analysis of data and draft the paper; Feng Zhang contributes to the acquisition of UK biobank data and agree all aspects of the work in ensuring the work to be appropriately investigated and resolved.

Author Contribution

Chun'e Li had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Chun'e Li and Feng Zhang.

Acquisition, analysis, or interpretation of data: Chun'e Li.

Drafting of the manuscript: Chun'e Li and Xiao Liang.

Critical revision of the manuscript for important intellectual content: All the authors.

Statistical analysis: Chun'e Li and Huijie Zhang.

Supervision: Feng Zhang.

Data Availability

All data analyzed during this study are included in the UK Biobank [https://nealelab.github.io/UKBB_ldsc/downloads.html] and the Digitalhub [https://digitalhub.northwestern.edu/collections/].

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Figures

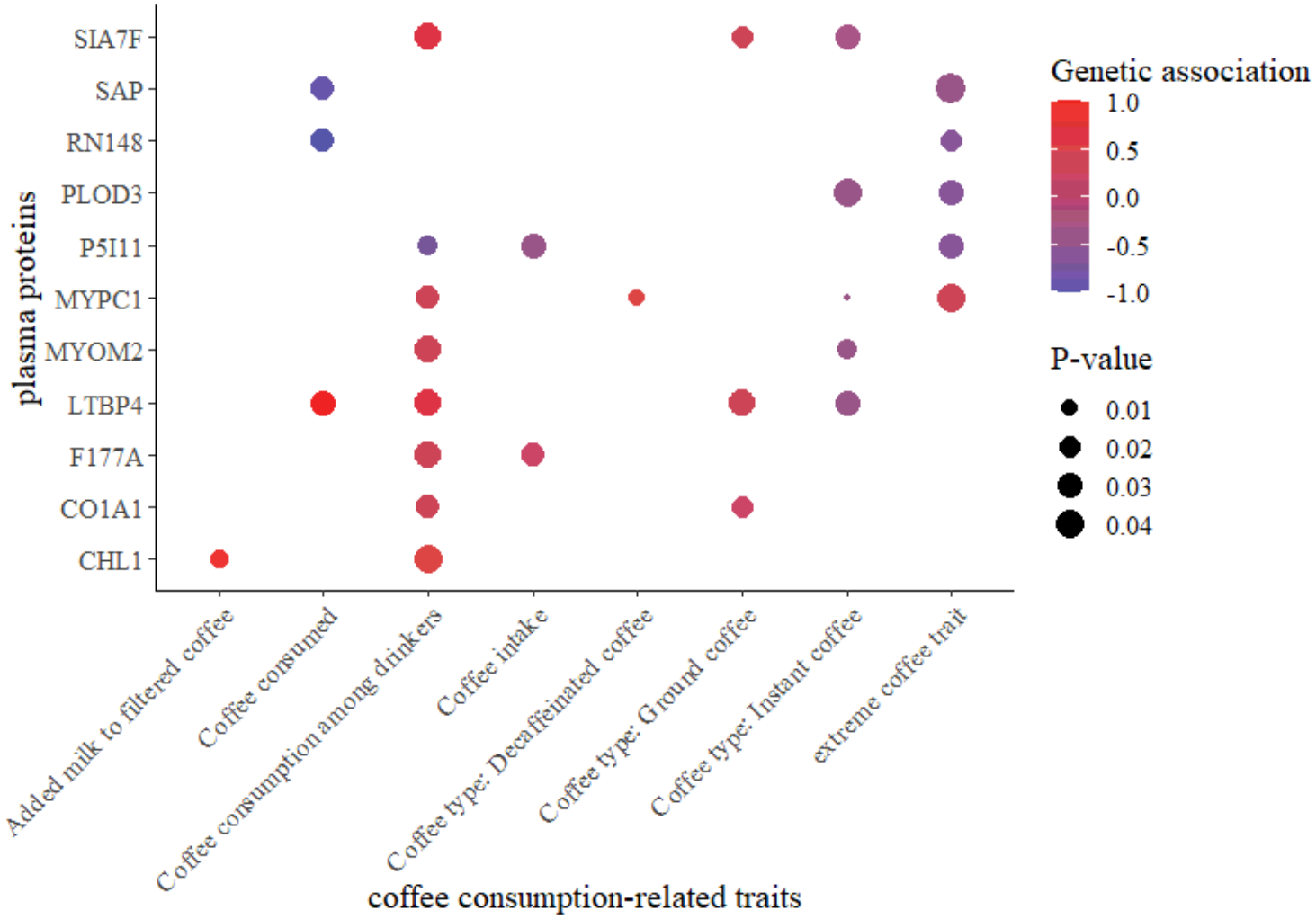


Figure 1

Genetic correlation between coffee consumption-related traits and plasma proteins. For the plot, the x-axis represents the coffee consumption-related traits, the y-axis represents the plasma proteins that overlap between the discovery cohort and the replication cohort, the color of the dots represents the genetic association, and the size of the dots represents the significant P value of the genetic association.

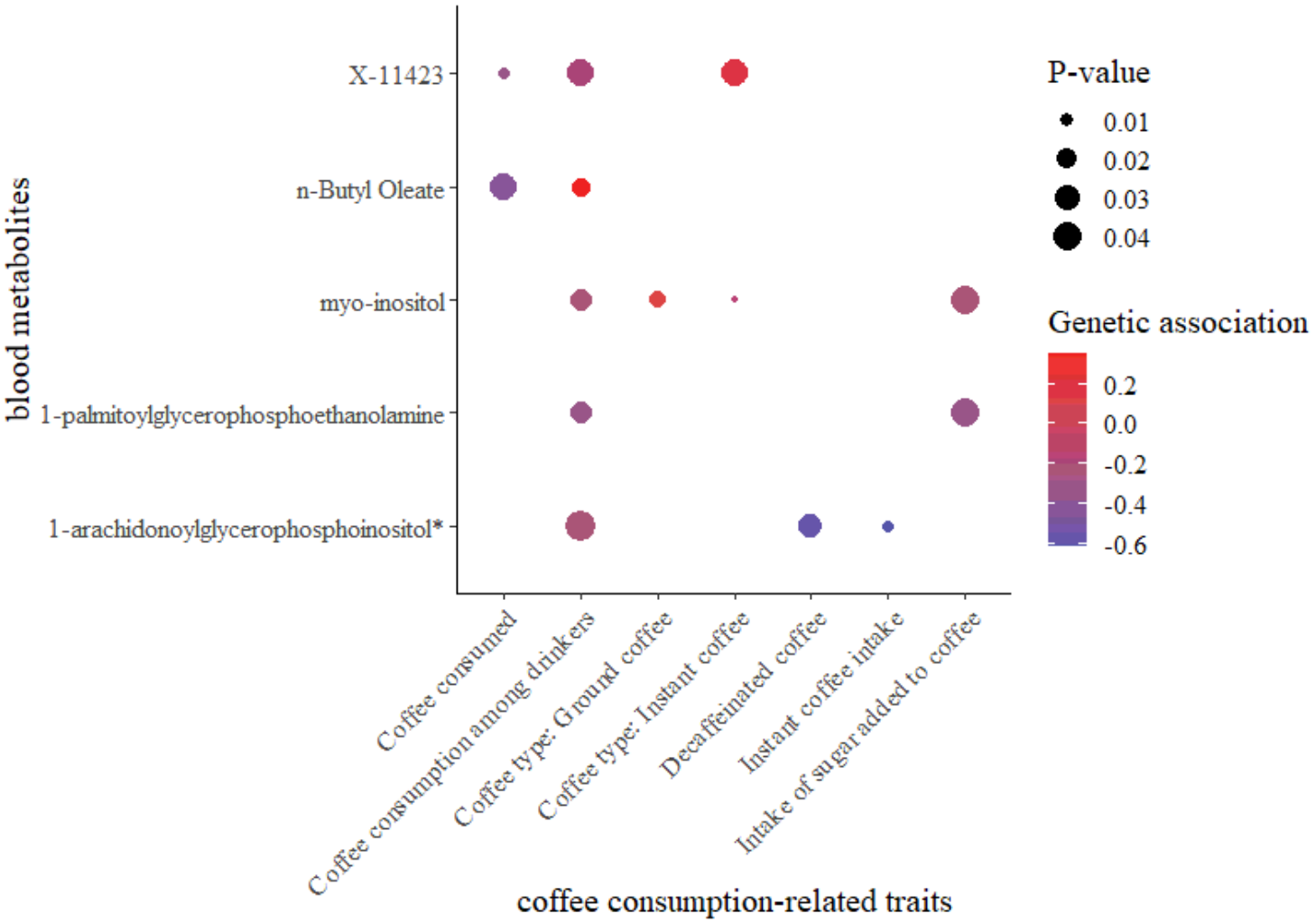


Figure 2

Genetic correlation between coffee consumption-related traits and blood metabolites. For the plot, the x-axis represents the coffee consumption-related traits, the y-axis represents the blood metabolites that overlap between the discovery cohort and the replication cohort, the color of the dots represents the genetic association, and the size of the dots represents the significant P value of the genetic association.

Supplementary Files

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- supplementary.xlsx