Molecular Psychiatry (2015) 20, 647–656

www.nature.com/mp

ORIGINAL ARTICLE

Genome-wide meta-analysis identifies six novel loci associated with habitual coffee consumption

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Coffee, a major dietary source of caffeine, is among the most widely consumed beverages in the world and has received considerable attention regarding health risks and benefits. We conducted a genome-wide (GW) meta-analysis of predominately regular-type coffee consumption (cups per day) among up to 91 462 coffee consumers of European ancestry with top single-nucleotide polymorphisms (SNPs) followed-up in ~30 062 and 7964 coffee consumers of European and African-American ancestry, respectively. Studies from both stages were combined in a trans-ethnic meta-analysis. Confirmed loci were examined for putative functional and biological relevance. Eight loci, including six novel loci, met GW significance ($\log_{10}$Bayes factor (BF) > 5.64) with per-allele effect sizes of 0.03–0.14 cups per day. Six are located in or near genes potentially involved in pharmacokinetics (*ABCG2*, *AHR*, *POR* and *CYP1A2*) and pharmacodynamics (*BDNF* and *SLC6A4*) of caffeine. Two map to *GCKR* and *MLXIPL* genes related to metabolic traits but lacking known roles in coffee consumption. Enhancer and promoter histone marks populate the regions of many confirmed loci and several potential regulatory SNPs are highly correlated with the lead SNP of each. SNP alleles near *GCKR*, *MLXIPL*, *BDNF* and *CYP1A2* that were associated with higher coffee consumption have previously been associated with smoking initiation, higher adiposity and fasting insulin and glucose but lower blood pressure and favorable lipid, inflammatory and liver enzyme profiles ($P < 5 \times 10^{-8}$).Our genetic findings among European and African-American adults reinforce the role of caffeine in mediating habitual coffee consumption and may point to molecular mechanisms underlying inter-individual variability in pharmacological and health effects of coffee.

Molecular Psychiatry (2015) **20,** 647–656; doi:10.1038/mp.2014.107; published online 7 October 2014

INTRODUCTION

Coffee is among the most widely consumed beverages in the world.[1] North American coffee drinkers typically consume ~2 cups per day while the norm is at least 4 cups in many European countries.[1] In prospective cohort studies, coffee consumption is consistently associated with lower risk of Parkinson's disease, liver disease and type 2 diabetes.[2] However, the effects of coffee on cancer development, cardiovascular and birth outcomes and other health conditions remain controversial.[2] For most populations, coffee is the primary source of caffeine, a stimulant also present in other beverages, foods and medications.[1,3] The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders does not include a diagnosis of caffeine dependence or abuse due to a paucity of evidence but lists caffeine intoxication and withdrawal as disorders.[4] Knowledge of factors contributing to coffee's consumption and physiological effects may greatly advance the design and interpretation of population and clinical research on coffee and caffeine.[5] Genetic factors could be especially valuable as they offer ways to study the potential health effects of coffee *via* instrumental variables or gene–environment interactions.[5] Heritability estimates for coffee and caffeine use range between 36 and 58%.[6] Genome-wide association studies (GWAS) of habitual caffeine and coffee intake have identified variants near *CYP1A2* and aryl hydrocarbon receptor (*AHR*).[7–9] Cytochrome P450 (CYP)1A2 is responsible for ~95% of caffeine metabolism in humans and AHR has a regulatory role in basal and substrate-induced expression of target genes, including *CYP1A1* and *CYP1A2*.[10,11]

To identify additional loci, we conducted a staged genome-wide (GW) meta-analysis of coffee consumption including over 120 000 coffee consumers sourced from population-based studies of European and African-American ancestry.

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Received 23 March 2014; revised 17 July 2014; accepted 22 July 2014; published online 7 October 2014

MATERIALS AND METHODS

Study design and populations

Supplementary Figure S1 depicts an overview of the current study. We performed a meta-analysis of GWAS summary statistics from 28 population-based studies of European ancestry to detect single-nucleotide polymorphisms (SNPs) that are associated with coffee consumption. Top loci were followed-up in studies of European (13 studies) and African-American (7 studies) ancestry and confirmed loci were explored in a single Pakistani population. Detailed information on study design, participant characteristics, genotyping and imputation for all contributing studies are provided in the Supplementary Information and Supplementary Tables S1–S6.

Phenotype

All phenotype data were previously collected *via* interviewer- or self-administered questionnaires (Supplementary Table S1). Our primary phenotype ('phenotype 1') was cups of predominately regular-type coffee consumed per day among coffee consumers. 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). A secondary analysis was performed comparing high with infrequent/non-coffee consumers ('phenotype 2'). A subset of stage 1 studies collected information on decaffeinated coffee consumption; which was examined in follow-up analysis of the confirmed loci.

Statistical analysis

Each stage 1 (discovery) study performed GWA testing for each phenotype across ~2.5 million genotyped or imputed autosomal SNPs (HapMap II, Centre d'Etude du Polymorphisme Humain (CEU) reference), based on linear (cups per day, phenotype 1) or logistic (high vs none/low, phenotype 2) regression under an additive genetic model. Analyses were adjusted for age, smoking status and, when applicable, sex, case–control status, study site, family structure and/or study-specific principal components of population substructure (Supplementary Table S7). SNPs with minor allele frequency < 0.02 or with low imputation quality scores were removed before meta-analysis (Supplementary Table S5). The GWAtoolbox (see Supplementary Information for URLs) was used for initial quality control. Minor allele frequencies and a plot comparing (1/median standard error of effect size) vs (square root of sample size) for each study were also reviewed for outliers and these were addressed before the final meta-analysis.

For both phenotypes, GW meta-analysis was conducted using a fixed-effects model and inverse-variance weighting with a single genomic control correction as implemented in METAL[12] and GWAMA[13] ($r > 0.99$ for correlation between METAL and GWAMA results). The phenotypic variance explained by additive SNP effects was estimated in the Women's Genome Health Study (WGHS, $n = 15\,987$ with identity-by-state < 0.025) using GCTA.[14] Stage 1 summary statistics were also subjected to pathway analysis using MAGENTA[15] (Supplementary Information).

For regions achieving association *P*-values $< 5 \times 10^{-8}$ (7p21, 7q23.11, 11p13 and 15q24), we performed conditional analysis using the summary statistics from the meta-analysis to test for the association of each SNP while conditioning on the top SNPs, with correlations between SNPs due to linkage disequilibrium (LD) estimated from the imputed genotype data from the Atherosclerosis Risk in Communities cohort,[16] a large and representative cohort of men and women of European ancestry.

Our approach to select SNPs for replication (stage 2) is described in Supplementary Information. Stage 2 meta-analyses were performed separately for European and African-American populations, using the same statistical models and methods as described for stage 1, but without genomic control (Supplementary Information).

Studies from all stages were included in an overall meta-analysis using MANTRA (Meta-ANalysis of TRans-ethnic Association) studies ;[17] which adopts a Bayesian framework to combine results from different ethnic groups by taking advantage of the expected similarity in allelic effects between the most closely related populations. MANTRA was limited to SNPs selected for replication thus no genomic control was applied. A random-effects analysis using GWAMA was performed in parallel to obtain effect estimates, which are not generated by MANTRA. The GW-significance threshold of $\log_{10}$ BF > 5.64 approximates a traditional GW *P*-value threshold of 5×10^{-8} under general assumptions.[18,19] Subgroup analysis and meta-regression were performed to investigate possible sources of between-study heterogeneity (Supplementary Information).

Fine-mapping. To assess the improvement in fine-mapping resolution due to trans-ethnic meta-analysis, we applied the methods of Franceschini *et al.*[17] to stage 1 and stage 2 (African Americans only) GW-summary level data (Supplementary Information).

Potential SNP function and biological and clinical inferences

Details pertaining to follow-up of confirmed loci are provided in the Supplementary Information. Briefly, all confirmed index SNPs and their correlated proxies were examined for putative function using publicly available resources. Bioinformatics and computational tools were used to systematically mine available knowledge and experimental databases to inform biological hypotheses underlying the link between loci and coffee consumption as well as connections between loci. For these analyses all genes mapping to the confirmed regions were considered as potential candidates. Finally, we searched the National Human Genome Research Institute GWAS catalog[20] and Metabolomics GWAS server[21] for all GW-significant associations with our confirmed coffee SNPs. Complete GWAS summary data for coffee-implicated diseases or traits were additionally queried.

RESULTS

SNPs associated with coffee consumption

Discovery stage. Results from the discovery stage are summarized in Supplementary Figures S2–S5. Little evidence for genomic inflation ($\lambda < 1.07$) was observed for either phenotype. The two analyses yielded similarly ranked loci and significant enrichment of 'xenobiotic' genes (MAGENTA's FDR < 0.006), suggesting no major difference in the genetic influence on coffee drinking initiation compared with the level of coffee consumption among coffee consumers at these loci. Overall, ~7.1% (standard error: 2%) of the variance in coffee cups consumed per day (phenotype 1) could be explained by additive and common SNP effects in the WGHS.

Conditioning on the index SNPs of each region achieving association *P*-values $< 5 \times 10^{-8}$ (7p21, 7q23.11, 11p13 and 15q24) in the discovery stage provided little evidence for multiple independent variants (Supplementary Figure S6). Only four of the SNPs on chromosome 7 were potentially independent and carried forward with other promising SNPs.

Replication and trans-ethnic meta-analysis. Forty-four SNPs spanning thirty-three genomic regions met significance criteria for candidate associations and were followed-up in stage 2 (Supplementary Tables S8–S13). Eight loci, including six novel, met our criteria for GW significance ($\log_{10}$ BF > 5.64) in a trans-ethnic meta-analysis of all discovery and replication studies (Table 1; Supplementary Tables S14–S16; Supplementary Figures S7 and S8). Confirmed loci have effect sizes of 0.03–0.14 cups per day per allele and together explain ~1.3% of the phenotypic variance of coffee intake. We were underpowered to replicate these associations in a Pakistani population (Supplementary Information).

Functional and biological inferences

Enhancer (H3K4me1) and promoter (H3K4me3) histone marks densely populate many of these regions and several non-synonymous and potential regulatory SNPs are highly correlated ($r^2 > 0.8$) with the lead SNP and thus strong candidates for being a causal variant (Table 2; Supplementary Information; Supplementary Tables S17–S19). Candidate genes form a highly connected network of interactions, featuring discernible clusters of genes around brain-derived neurotrophin factor (*BDNF*) and *AHR* (Figure 1; Supplementary Information; Supplementary Tables S20 and S21). At least one gene in each of the eight regions (i) is highly expressed in brain, liver and/or taste buds, (ii) results in phenotype abnormalities relevant to coffee consumption behavior when modified in mice and (iii) is differentially expressed in human hepatocytes when treated with high (7500 μM) but not low (1500 μM) doses of caffeine (Table 2; Supplementary Tables S22–S24).

Table 1. SNPs associated with cups of coffee consumed per day among coffee consumers

Locus	*Index SNP*[a]	*Closest gene*	*EA/NEA*	*EAF EUR/AA*	*Stage 1*[b] *EUR* n ⩽ *91 462*		*Stage 2*[b]				*Trans-ethnic meta-analysis*[c]			
							EUR n ⩽ *30 062*		*AA* n ⩽ *7964*					
					β (s.e.)	P	*β (s.e.)*	P	*β (s.e.)*	P	*β (s.e.)*	*Log*$_{10}$*BF*	*Post Prob*	n
2p24	**rs1260326**	*GCKR*	T/C	0.41/0.17	−0.04 (0.01)	1.06×10^{-07}	−0.03 (0.01)	0.02	−0.01 (0.03)	0.77	−0.04 (0.01)	6.48	0.07	129 417
4q22	**rs1481012**	*ABCG2*	A/G	0.89/0.95	0.06 (0.01)	1.13×10^{-06}	0.03 (0.02)	0.11	0.16 (0.05)	1.27×10^{-03}	0.06 (0.01)	6.08	0.23	126 019
7p21	rs4410790	*AHR*	T/C	0.37/0.52	−0.14 (0.01)	1.48×10^{-57}	−0.05 (0.01)	1.66×10^{-04}	−0.09 (0.02)	2.37×10^{-06}	−0.10 (0.01)	58.87	0.96	116 674
	rs6968554		A/G	0.39/0.33	−0.13 (0.01)	2.54×10^{-57}	−0.07 (0.01)	2.78×10^{-10}	−0.05 (0.02)	0.02	−0.10 (0.01)	69.69	1.00	124 849
7q11.23	**rs7800944**	*MLXIPL*	T/C	0.72/0.67	−0.05 (0.01)	7.82×10^{-09}	−0.06 (0.02)	4.20×10^{-04}	−0.02 (0.02)	0.37	−0.05 (0.01)	8.83	0.09	116 417
7q11.23	**rs17685**	*POR*	A/G	0.29/0.19	0.07 (0.01)	9.06×10^{-14}	0.05 (0.01)	1.01×10^{-03}	0.07 (0.03)	7.55×10^{-03}	0.07 (0.01)	15.12	0.08	115 465
11p13	**rs6265**	*BDNF*	T/C	0.19/0.07	−0.05 (0.01)	3.40×10^{-07}	−0.03 (0.01)	0.07	−0.05 (0.04)	0.25	−0.04 (0.01)	5.76	0.10	127 828
15q24	rs2470893	*CYP1A1*	T/C	0.31/0.06	0.12 (0.01)	6.89×10^{-44}	0.09 (0.01)	9.92×10^{-11}	0.20 (0.07)	4.23×10^{-03}	0.12 (0.01)	57.79	1.00	113 273
	rs2472297	*CYP1A2*	T/C	0.24/0.06	0.15 (0.01)	6.45×10^{-47}	0.11 (0.01)	3.26×10^{-16}	0.19 (0.05)	8.62×10^{-05}	0.14 (0.01)	62.77	0.97	116 272
17q11.2	**rs9902453**	*EFCAB5*	A/G	0.54/0.80	−0.04 (0.01)	2.26×10^{-06}	−0.03 (0.01)	9.13×10^{-03}	−0.04 (0.03)	0.17	−0.03 (0.01)	6.29	0.05	126 819

Abbreviations: AA, African-American ancestry; BF, Bayes-factor; EA, effect allele; EAF, effect allele frequency; EUR, European ancestry; NEA, non-effect allele; Post Prob, posterior probability; SNP, single-nucleotide polymorphism. [a]Genic SNPs are in boldface. [b]Effect coefficients (s.e.), representing cups per day per effect allele, and corresponding *P*-values from stage 1 fixed-effects meta-analysis (columns 6 and 7) and stage 2 fixed-effects meta-analyses (columns 8–11). [c]Effect coefficients (s.e.), representing cups per day per effect allele, from random-effects meta-analysis of all stage 1 and stage 2 studies (column 12). $Log_{10}BF$ (column 13) and the corresponding posterior probabilities (column 14) from trans-ethnic meta-analysis of all stage 1 and stage 2 studies. A posterior probability of >0.5 suggests heterogeneity in allelic effects.

Additional genomic characterization of the top loci allows further biological inference as follows:

(i) Previously identified loci near AHR (7p21) and CYP1A2 (15q24). Consistent with previous reports in smaller samples,[7–9] the intergenic 7p21 and 15q24 loci near *AHR* and *CYP1A1/CYP1A2* respectively remained the most prominent and highly heterogeneous loci associated with coffee consumption. The same index SNPs were identified in European and African Americans, suggesting that they are robust HapMap proxies for causal variants in these two populations. Cohort-wide mean coffee consumption explained part of the heterogeneity in study results for both loci (Supplementary Table S25; Supplementary Information). The rs2472297 T and rs4410790 C alleles associated with increased coffee consumption have recently been associated with lower plasma caffeine levels[21] and shown to increase CYP1A2-mediated metabolism of olanzapine.[22] The C allele of rs4410790 is also positively correlated with cerebellum *AHR* methylation, suggesting a novel role of Ahr in motor or learning pathways that may trigger coffee consumption. The most significant variants at 15q24 reside in the *CYP1A1-CYP1A2* bidirectional promoter where *AHR* response elements have been identified and shown to be important for transcriptional activation of both *CYP1A1* and *CYP1A2*.[23] The rs2472297 T variant putatively weakens the binding of SP1, a co-activator in the Ahr–Arnt complex regulating CYP1 locus transcription[24] and is also implicated in the expression of several neighboring genes. The latter observation, together with this region's high LD and long range chromatin interactions (Supplementary Figure S9), suggests a regulatory network among these genes.

(ii) Novel loci at 7q11.23 (POR) and 4q22 (ABCG2) likely function in caffeine metabolism. Variants at 7q11.23 (rs17685) and 4q22 (rs1481012) map to novel yet biologically plausible candidate genes involved in xenobiotic metabolism. rs17685 maps to the 3′UTR of *POR*, encoding P450 oxidoreductase which transfers electrons to all microsomal CYP450 enzymes.[25] The rs17685 A variant associated with higher coffee consumption is linked to increased *POR* expression and potentially weakens the DNA binding of several transcriptional regulatory proteins including BHLHE40, which inhibits *POR* expression.[26] The same SNP is in LD (CEU: $r^2=0.93$) with *POR*28* (rs1057868 and Ala503Val), which is associated with differential CYP activity depending on the CYP isoform, substrate and experimental model used.[27] rs1481012 at 4q22 maps to *ABCG2*, encoding a xenobiotic efflux transporter. rs1481012 is in LD (CEU: $r^2=0.92$) with rs2231142 (Gln141Lys), a functional variant at an evolutionarily constrained residue.[28] However, fine-mapping of this region on the basis of reduced LD in the African-American sample limited an initial 189 102-kb region to a credible span of 6249 kb (Supplementary Table S16) that excluded rs2231142.

(iii) Novel loci at 11p13 (BDNF) and 17q11.2 ('SLC6A4') likely mediate the positive reinforcing properties of coffee constituents. The index SNP at 11p13 is the widely investigated missense mutation (rs6265 and Val66Met) in *BDNF* (Supplementary Table S26). BDNF modulates the activity of serotonin, dopamine and glutamate, and neurotransmitters involved in mood-related circuits and have a key role in memory and learning.[29] The Met66 allele impairs neuronal activity-dependent BDNF secretion[30] and thus may attenuate the rewarding effects of coffee and, in turn, motivation to consume coffee. The increasingly recognized roles of BDNF in the chemosensory system and conditioned taste preferences may also be relevant.[31] The index SNP (rs9902453) at 17q11.2 maps to the *EFCAB5* gene and is in LD (CEU: $r^2>0.8$) with SNPs that alter regulatory motifs for AhR[32] in the neighboring gene *NSRP1*, but neither gene is an obvious candidate for coffee consumption. Upstream of rs9902453 lies a possibly stronger candidate: *SLC6A4*

Table 2. Potential function of loci associated with coffee consumption[a]

Locus	*Gene expression response to caffeine*[b]	*Lead-SNP, allele ↑coffee consumption*[c]	*Non-Syn SNPs in LD*[d]	*CR*[e]	*DNAse*[f]	*Proteins bound*[g]	*Histone marks*[h]	*Motifs changed*[i]	*eQTL*[j]	*mQTL*[k]
2p24	*GCKR, CCDC121, FNDC4, ZNF513, SNX17, PPM1G, GPN1, SUPT7L, MPV17, SLC4A1AP, PREB, ATRAID, GTF3C2*	rs1260326, C	Leu446Pro	✓	✓	✓	Enhancer	NRSF	*EIF2B4, SNX17, NRBP1*	*KRTCAP3, PPM1G*
4q22	*ABCG2, SPP1*	rs1481012, A	✓	✓	✓	✓	Enhancer	AIRE, Zfp105		
7p21	*AHR*	rs4410790, C rs6968554, G		✓	✓			Cdx2, DMRT3, E4BP4, Foxa, GR, Hoxa10, Hoxa9, Hoxb13, Hoxb9, Hoxc9, Hoxd10, Myc, p300, TR4		*AHR*
7q11.23	*MLXIPL, BCL7B, DNAJC30, TBL2, WBSCR22*	rs7800944, C			✓	✓	Promoter enhancer	AP-4, BHLHE40, GATA,GR, Irf, Pax-5	*WBSCR22, MLXIPL*	*FZD9*
7q11.23	*RHBDD2, POR STYXL1, TMEM120A, MDH2, HSPB1*	rs17685, A	✓	✓	✓	✓		Arnt, BHLHE40, DEC,Ets, Mxi1,Myc, Pax-5, Sin3Ak-20, TFE	*RHBDD2, POR, TMEM120A, STYXL1, MDH2*	*STYXL1*
11p13	*CCDC34, LIN7C, METTL15,*	rs6265, C	Val66Met	✓	✓	✓	Promoter enhancer	BHLHE40, Myc, SREBP		
15q24	*PPCDC, ARID3B, ULK3, SEMA7A, EDC3, COX5A, CSK, RPP25, MPI*	rs2470893, T rs2472297, T						SP1	*MPI, SCAMP2, ULK3, ISLR, SNUPN, RPP25, CSK,*	*SCAMP2*
17q11.2	*TAOK1, SLC6A4 NSRP1, BLMH*	rs9902453, G	✓	✓	✓	✓	Promoter enhancer	STAT	*GIT1, ATAD5, SLC6A4*	*NSRP1, ANKRD13B, CRLF3, CORO6*

Abbreviations: CEU, Centre d'Etude du Polymorphisme Humain; CR, conserved region; eQTL, expression quantitative trait loci; LD, linkage disequilibrium; mQTL, methylation quantitative trait loci; SNP, single-nucleotide polymorphism. [a]See Supplementary Information for details and references to data resources. [b]*In vitro* human hepatic gene expression in response to caffeine. Red and green font corresponds to increased and decreased expression, respectively. [c]Lead SNP allele associated with *higher* coffee consumption. [d]Check marks (✓) denote the *presence* of non-synonymous SNPs in LD (CEU: $r^2 \geqslant 0.80$) with lead SNP (details provided for lead SNP only). [e]Check marks (✓) denote the *presence* of a conserved region (spanning lead SNP and its correlated proxies, CEU: $r^2 \geqslant 0.8$). [f]Check marks (✓) denote the *presence* of DNAse hypersensitivity sites at region spanning lead SNP and its correlated proxies, CEU: $r^2 \geqslant 0.8$. [g]Check marks (✓) denote the *presence* of proteins bound at region spanning lead SNP and its correlated proxies, CEU: $r^2 \geqslant 0.8$. [h]Enhancer (H3K4me1) or promoter (H3K4me3) histone marks (as defined by Ernst *et al.*[32]) spanning lead SNP and its correlated proxies, CEU: $r^2 \geqslant 0.8$. [i]Regulatory motifs altered by lead SNP. [j]Expression QTLs for lead SNP or perfect proxy (CEU: $r^2 = 1$) derived from lymphoblastoid cell lines, blood, or liver, adipose and brain tissues. Red and green font corresponds to increased and decreased expression, respectively, relative to allele associated with *higher* coffee consumption. Direction of *GITI* expression is not available. [k]Methylation QTLs for lead SNP derived from cerebellum and frontal cortex. Red and green font corresponds to increased and decreased expression, respectively, relative to allele associated with *higher* coffee consumption.

encoding the serotonin transporter. Serotonergic neurotransmission affects a wide range of behaviors including sensory processing and food intake.[33]

(iv) Novel loci at 2p24 (GCKR) and 17q11.2 (MLXIPL). Variants at 2p24 (rs1260326) and 7q11.23 (rs7800944) map to *GCKR* and *MLXIPL*, respectively. The former has been associated with plasma glucose and multiple metabolic traits and the latter with plasma triglycerides (Table 3; Supplementary Table S27). Adjustment of regression models for plasma lipids in the WGHS ($n \sim 17\,000$) and plasma glucose in TwinGene ($n \sim 8800$) did not significantly change the relationship between SNPs at these two loci and coffee consumption ($P > 0.48$, Supplementary Tables S28 and S29). The rs1260326 T allele encodes a non-synonymous change in the encoded, glucokinase regulatory protein leading to increased hepatic glucokinase activity.[34] Glucokinase regulatory protein and glucokinase may also cooperatively function in the glucose-sensing process of the brain[35] that may, in turn, influence central pathways responding to coffee constituents. A direct link between *MLXIPL* and coffee consumption remains unclear, except for the interactions with other candidate genes (Figure 1). Experimental evidence and results from formal prioritization analyses also warrants consideration of other candidates in these regions (Figure 1; Table 2; Supplementary Tables S23). For example, in the frontal cortex, the rs1260326 allele positively associated with coffee consumption correlates with lower methylation of *PPM1G*; a putative regulatory target for AhR and binding target for *PPP1R1B*, which mediates psychostimulant effects of caffeine.[36]

Pleiotropy and clinical inferences

None of the eight loci was significantly associated with caffeine taste intensity ($P > 0.02$) or caffeine-induced insomnia ($P > 0.08$), according to previously published GWAS of these traits.[37–39] SNPs near *AHR* associated with higher coffee consumption were also significantly associated with higher decaffeinated coffee consumption (~0.05 cups per day, $P < 0.0004$, $n = 24\,426$); perhaps a result of Pavlovian conditioning among individuals moderating their intake of regular coffee or the small amounts of caffeine in decaffeinated coffee.[1]

Across phenotypes in the GWAS catalog,[20] the alleles leading to higher coffee consumption at 2p24, 4q22, 7q11.23, 11p13 and 15q24 have been associated with one or more of the following: smoking initiation, higher adiposity and fasting insulin and glucose but lower blood pressure and favorable lipid, inflammatory and liver enzyme profiles ($P < 5 \times 10^{-8}$, Table 3; Supplementary Table S27). Focused on metabolic, neurologic and psychiatric traits for which coffee has been implicated (Table 3; Supplementary Table S32), there were additional sub-GW significant associations in published GWAS. Variants associated with higher coffee consumption increased adiposity (rs1481012, $P = 4.85 \times 10^{-3}$), birth weight (rs7800944, $P = 2.10 \times 10^{-3}$), plasma high-density lipoprotein (HDL, rs7800944, $P = 2.24 \times 10^{-3}$), risk of Parkinson's disease (rs1481012, $P = 7.11 \times 10^{-3}$), reduced blood pressure (rs6265, $P = 6.58 \times 10^{-4}$; rs2472297, $P < 6.80 \times 10^{-5}$ and rs9902453, $P = 6.05 \times 10^{-3}$), HDL (rs6968554, $P = 1.18 \times 10^{-3}$), risk of major depressive disorder (rs17685, $P = 6.98 \times 10^{-3}$) and bipolar disorder (rs1260326, $P = 2.31 \times 10^{-3}$). Associations with adiposity, birth weight, blood pressure, HDL and bipolar disorder remain significant after correcting for the number of SNPs tested.

DISCUSSION

Coffee's widespread popularity and availability has fostered public health concerns of the potential health consequences of regular coffee consumption. Findings from epidemiological studies of

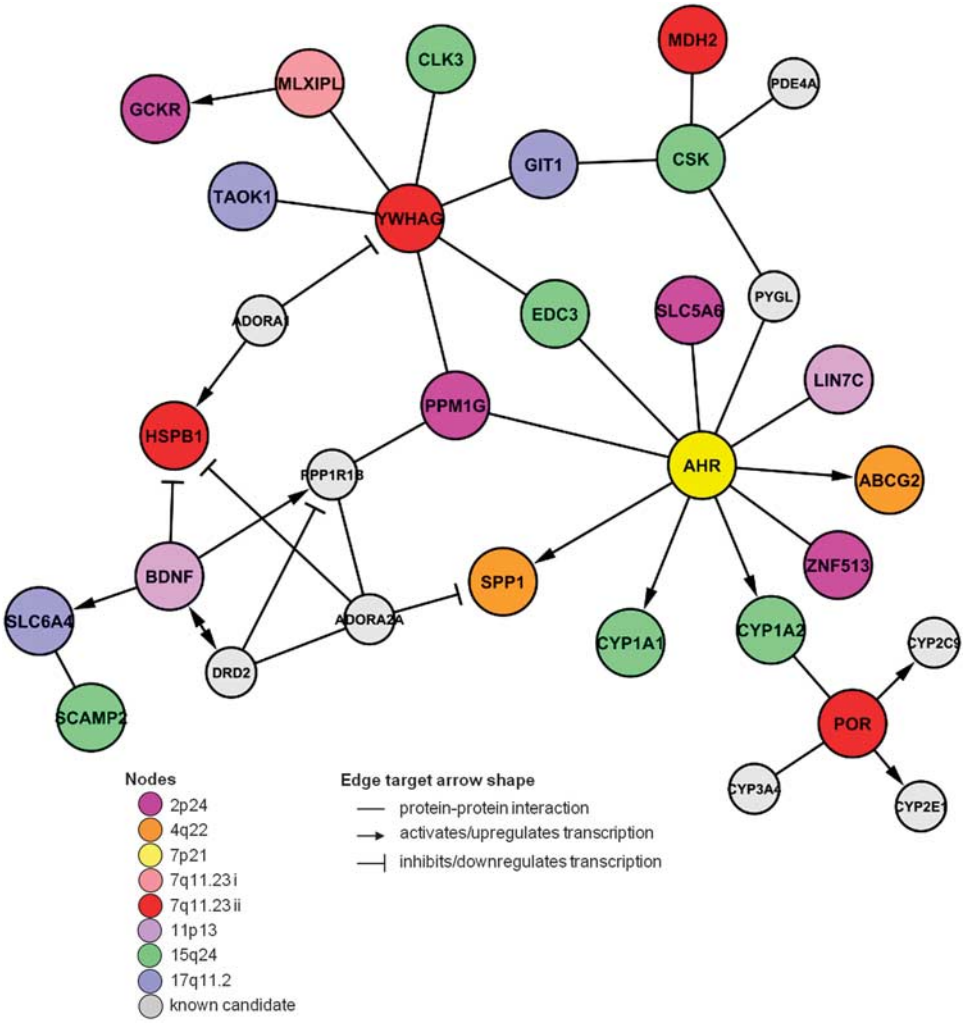

Figure 1. Network describing direct interactions between candidate genes of confirmed loci. Relationships were retrieved from databases of transcription regulation and protein–protein interaction experiments (Supplementary Table S21). Genes are represented as nodes that are colored according to locus. Candidate genes for loci identified in the current study were supplemented with known candidate genes related to caffeine pharmacology (gray nodes). Edges indicate known interactions.

coffee consumption and certain health conditions remain controversial.[2] Knowledge of genetic factors contributing to coffee's consumption and physiological effects may inform the design and interpretation of population and clinical research on coffee.[5] In the current report, we present results of the largest GWAS of coffee intake to-date and the first to include populations of African-American ancestry. In addition to confirming associations with *AHR* and *CYP1A2*, we have identified six new loci, not previously implicated in coffee drinking behavior.

Our findings highlight an important role of the pharmacokinetic and pharmacodynamic properties of the caffeine component of coffee underlying a genetic propensity to consume the beverage. Loci near *BDNF* and *SLC6A4* potentially impact consumption behavior by modulating the acute behavioral and reinforcing properties of caffeine. Others near *AHR*, *CYP1A2*, *POR* and *ABCG2* act indirectly by altering the metabolism of caffeine and thus the physiological levels of this stimulant. The strength of these four associations with coffee intake, along with results from pathway analysis showing significant enrichment for 'xenobiotic' genes, emphasize an especially pronounced role of caffeine metabolism in coffee drinking behavior. The current study is the first to link *GCKR* and *MLXIPL* variation to a behavioral trait. The non-synonymous rs1260326 SNP in *GCKR* has been a GW signal for various metabolic traits particularly those reflecting glucose homeostasis (Table 3). *GCKR* variation may impact the glucose-sensing process of the brain[35] that may, in turn, influence central pathways responding to coffee constituents. Methylation quantitative trait loci and binding motif analysis suggest that *PPM1G* may be another candidate underlying the association between rs1260326 and coffee consumption. Variants near *MLXIPL* have also topped the list of variants associated with plasma triglycerides (Table 3), but their link to coffee consumption remains unclear. Future studies on the potential pleiotropic effects of these two loci are clearly warranted. Interestingly, several candidate genes implicated in coffee consumption behavior, but not confirmed in our GWAS, interact with one or more of the eight confirmed loci (Figure 1). While these findings are encouraging for ongoing efforts they also emphasize the need to study sets or pathways of genes in the future.

Specific SNPs associated with higher coffee consumption have previously been associated with smoking initiation, higher adiposity and fasting insulin and glucose but lower blood pressure and favorable lipid, inflammatory and liver enzyme profiles. Whether these relationships reflect pleiotropy, confounding or

Table 3. Associations between coffee consumption loci and other traits

Lead SNP, allele ↑ coffee consumption[a]	*Other traits*[b]	
closest gene	*Higher levels/risk*[c]	*Lower levels/risk*[c]
rs1260326, C *GCKR*	Non-albumin protein Fasting glucose HOMA-IR Fasting insulin Mannose	Serum albumin 2-H glucose challenge Metabolic syndrome Glucose/mannose ratio Total cholesterol Triglycerides Hypertriglyceridemia Chronic kidney disease Uric acid SHBG Crohn's disease C-reactive protein Platelet counts GGT Docosapentaenoic acid Alanine/glutamine ratio Alanine
		LDL ($P = 2.33 \times 10^{-4}$) Waist-to-hip-ratio ($P = 3.40 \times 10^{-4}$) Bipolar disorder ($P = 2.31 \times 10^{-3}$)
rs1481012, A *ABCG2*		LDL response to statins ('responders') Uric acid
	Body mass index ($P = 4.85 \times 10^{-3}$)	
rs6968554, G *AHR*		Caffeine
		HDL ($P = 1.18 \times 10^{-3}$)
rs7800944, C *MLXIPL*		triglycerides
	HDL ($P = 2.24 \times 10^{-3}$) Birth weight ($P = 2.10 \times 10^{-3}$)	
rs6265, C *BDNF*	Smoking initiation Body mass index	
		DBP ($P = 6.58 \times 10^{-4}$)
rs2472297[d], T *CYP1A1_CYP1A2*		*Caffeine*[e]
		SBP ($P = 6.81 \times 10^{-5}$) DBP ($P = 6.75 \times 10^{-6}$)
rs9902453, G *EFCAB5*		SBP ($P = 6.05 \times 10^{-3}$)

Abbreviations: CEU, Centre d'Etude du Polymorphisme Humain; DBP, diastolic blood pressure; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein; LD, linkage disequilibrium; LDL, low-density lipoprotein; SBP, systolic blood pressure; SHBG, sex hormone binding globulin; SNP, single-nucleotide polymorphism. [a]Lead SNP allele associated with *higher* coffee consumption. [b]Traits associated with lead SNP (or close proxies: $r^2 > 0.80$) according to previous GWAS[20] (Shin *et al.*[21]). Gray cells denote all GW-significant significant associations ($P < 5.00 \times 10^{-8}$ [20] or $P < 1.03 \times 10^{-10}$ (Shin *et al.*[21]) and white cells denote coffee-relevant trait associations ($P < 6.25 \times 10^{-3}$). See Supplementary Information for details and references to original GWAS. [c]Relative to allele associated with *higher* coffee consumption. [d]rs1378942 A, also associated with higher coffee consumption ($P < 1.46 \times 10^{-17}$) in stage 1 of the current report but in low LD with rs2472297 (CEU: $r^2 = 0.10$), was previously associated with lower DBP in GWAS ($P < 5.00 \times 10^{-8}$). [e]Borderline significant ($P < 1.51 \times 10^{-10}$) according to Shin *et al.*[21]

offer insight to the potential causal role coffee plays in these traits merits further investigation. Future research, particularly Mendelian Randomization and gene–coffee interaction studies, will need to consider the direct and indirect roles that each SNP has in altering coffee drinking behavior as well as the potential for interactions between loci (Figure 1). The heterogeneous effects specific to *AHR*- and *CYP1A2*-coffee associations point to SNP-specific interactions with the environment or population characteristics that might also warrant consideration (Supplementary Information).

The strong cultural influences on norms of coffee drinking may have reduced our power for loci discovery. This might, in part, underlie our lack of replication in a Pakistani population, wherein coffee consumption is extremely rare. Methodological limitations specific to our approach may also have reduced our power for loci discovery or precision in estimating effect sizes (Supplementary Information). For example, some studies collected coffee data in categories of cups per day (for example, 2–3 cups per day) rendering a less precise record of intake as well as a non-Gaussian distributed trait for analysis. The precise chemical composition of different coffee preparations is also not captured by standard food frequency questionnaire and is likely to vary within and between populations. Nevertheless, the eight loci together explain ~1.3% of the phenotypic variance, a value *at least* as great as that reported for smoking behavior and alcohol consumption which are subjected to similar limitations in GWAS.[40,41]

The additive genetic variance (or narrow-sense heritability) of coffee intake as estimated by GCTA in WGHS (7%) is considerably lower than estimates based on pedigrees (36–57%).[6] The marked discrepancies between the GCTA and pedigree estimates of heritability may be due to one or more of the following: the potential contribution of rare variants to heritability (not captured by GCTA's 'chip-based heritability'), biases in pedigree analysis resulting in overestimates of heritability, differences in phenotype ascertainment or definition and cultural differences in the populations studied.[42]

In conclusion, our results support the hypothesis that metabolic and neurological mechanisms of caffeine contribute to coffee consumption habits. Individuals adapt their coffee consumption habits to balance perceived negative and reinforcing symptoms that are affected by genetic variation. Genetic control of this potential 'titrating' behavior would incidentally govern exposure to other potentially 'bioactive' constituents of coffee that may be related to the health effects of coffee or other sources of caffeine. Thus, our findings may point to molecular mechanisms underlying inter-individual variability in pharmacological and health effects of coffee and caffeine.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

Study-specific funding and acknowledgments are provided in the Supplementary Information. We collectively thank everyone who has contributed to the collection, genotyping and analysis of the individual cohorts, as well as all the study participants.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)

APPENDIX

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