

RESEARCH

Open Access



Transcriptome-wide association study identified candidate genes associated with gut microbiota

Chuyu Pan[†], Yujie Ning[†], Yumeng Jia, Shiqiang Cheng, Yan Wen, Xuena Yang, Peilin Meng, Chun'e Li, Huijie Zhang, Yujing Chen, Jingxi Zhang, Zhen Zhang and Feng Zhang*[✉]

Abstract

Background: Gut microbiota is closely associated with host health and disease occurrence. Host genetic factor plays an important role in shaping gut microbial communities. The specific mechanism of host-regulated gene expression affecting gut microbiota has not been elucidated yet. Here we conducted a transcriptome-wide association study (TWAS) for gut microbiota by leveraging expression imputation from large-scale GWAS data sets.

Results: TWAS detected multiple tissue-specific candidate genes for gut microbiota, such as FUT2 for genus *Bifidobacterium* in transverse colon ($P_{\text{PERM,ANL}} = 1.68 \times 10^{-3}$) and SFTPD for an unclassified genus of *Proteobacteria* in transverse colon ($P_{\text{PERM,ANL}} = 5.69 \times 10^{-3}$). Fine mapping replicated 3 candidate genes in TWAS, such as HELLS for *Streptococcus* (PIP = 0.685) in sigmoid colon, ANO7 for *Erysipelotrichaceae* (PIP = 0.449) in sigmoid colon. Functional analyses detected 94 significant GO terms and 11 pathways for various taxa in total, such as GO_NUCLEOSIDE_DIPHOSPHATASE_ACTIVITY for *Butyrivibrio* (FDR $P = 1.30 \times 10^{-4}$), KEGG_RENIN_ANGIOTENSIN_SYSTEM for *Anaerostipes* (FDR $P = 3.16 \times 10^{-2}$). Literature search results showed 12 genes prioritized by TWAS were associated with 12 diseases. For instance, SFTPD for an unclassified genus of *Proteobacteria* was related to atherosclerosis, and FUT2 for *Bifidobacterium* was associated with Crohn's disease.

Conclusions: Our study results provided novel insights for understanding the genetic mechanism of gut microbiota, and attempted to provide clues for revealing the influence of genetic factors on gut microbiota for the occurrence and development of diseases.

Keywords: Gut microbiota, Transcriptome-wide association study (TWAS), Genome-wide association study (GWAS), Pathway

Background

Gut microbiota is an enormous and complex ecosystem, which is closely associated with the host by affecting metabolism, immunity and other physiological functions

[1, 2]. Numerous studies have suggested that the correlation of gut microbiota with the incidence of complex diseases. A case-control study showed the microbial pattern of women with breast cancer is different from healthy women in terms of bacterial type, relative abundance and function [3]. A cohort study of Indian Children found that the proportion of *Firmicutes* in Autistic Spectrum Disorder (ASD) children was higher than healthy children [4]. In addition, the gut microbiota might involve in modulation of body mass index and blood lipid level according to the LifeLines-DEEP population cohort study

*Correspondence: fzhxjtu@mail.xjtu.edu.cn

[†]Chuyu Pan and Yujie Ning contributed equally to this work
Key Laboratory of Trace Elements and Endemic Diseases of National Health and Family Planning Commission, National Health Commission of the People's Republic of China, School of Public Health, Health Science Center, Xi'an Jiaotong University, Xi'an 71006, China



© The Author(s) 2021. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

which consists of 893 subjects [5]. However, the mechanism of a large part of diseases induced by gut microbiota is still unclear, needing further research to elucidate.

The composition of the gut microbiota is shaped by multiple factors including environment, diet, medication as well as internal parameters [6]. In recent decades, great deal of evidence has indicated that host genetic factor plays indispensable role in shaping the gut microbial communities. Lim et al. found monozygotic twin pairs had more similar gut microbial communities compared with other family members, and 50 gut microbial taxa (58.8%) showed significant heritability among the 85 taxa identified with heritability estimates valued ranging between 13.1% and 45.7% [7]. Additionally, based on a large ($n = 645$) mouse advanced intercross line, microbial quantitative trait loci (mbQTLs) could significantly affect gut microbial taxa [8]. Moreover, microbial genome-wide association analysis (mGWAS) has been conducted in recent years to reveal loci related to the gut microbiota. According to a previous study, *Lactococcus* bacteria could be affected by single nucleotide polymorphism (SNP) rs2294239 in ZNRF3 gene, which is associated with body fat distribution [9].

The gut microbiota can be regarded as a trait affected by genetic factors [8]. Although GWAS has contributed to a great number of genetic clues related to complex diseases and traits, it has limitation in explaining how the genetic variations regulate gene expression alone because the SNPs identified mainly located in non-coding regions [10]. In recent years, expression quantitative trait loci (eQTLs) have been widely used to elucidate the influence of genetic variants at gene expression level [11]. Subsequently, integrated analysis of GWAS and eQTLs became practical in exploring the effect of gene expression on complex traits [12]. One such family of methods is transcriptome-wide association study (TWAS), which was conducted to impute expression from genetic data, showing great power to prioritize candidate genes of complex traits interested, and has been used to identify the associations between many diseases and genes [13]. For example, Liao et al. identified KAT2B and TMEM161B as causal genes for attention deficit hyperactivity disorder by TWAS [14]. Another TWAS detected 25 genes, including CELA3B, whose predictive expression was statistically significantly associated with pancreatic cancer risk [15]. To the best of our knowledge, no TWAS was applied in gut microbiota study until now.

In this study, we performed TWAS analysis and fine mapping of gut microbiota for multiple tissues by leveraging expression imputation from large-scale GWAS data sets. Subsequently, functional analysis was conducted for exploration of the biological functions and pathways of significant gene sets. Furthermore, we sorted out diseases

associated with gut microbiota candidate genes by manually reviewing the literature.

Methods

mGWAS of gut microbiota

The human microbiota GWAS summary data were obtained from a study published by Hughes et al. [16]. The study projects consisted of 2223 individuals from the Flemish Gut Flora Project (FGFP) cohort. DNA was extracted from frozen fecal samples and used for 16S ribosomal RNA gene sequencing subsequently. Among 499 taxon-derived abundances in FGFP, 92 taxa met the analysis criteria, which were identified independent phenotypes. The presence/absence (P/A) phenotype (binary) and the zero-truncated (all zero values set as missing) abundance (AB) phenotype (continuous) were generated for taxa where $>5\%$ of individuals in FGFP had an abundance measurement of zero. The genome-wide genotyping of FGFP was conducted using either the Human Core Exome v.1.0 array or the Human Core Exome v.1.1 array. Snptest.2.5.0 was used for association analysis. In brief, 157 microbial traits, including 62 presence/absence (P/A-HB) and 95 in abundance (AB-RNT) microbial phenotypes were included in the subsequent analysis. Detailed information on subjects, study design, statistical analysis and quality control can be found in the publication [16].

TWAS of gut microbiota

TWAS of gut microbiota was performed by FUSION software, which precomputed the gene expression weights of various tissues using a small set of individuals with both gene expression and genotype data. The *cis*-genetic component of expression was then imputed into much larger sets of phenotyped individuals according to SNP genotype data. In this study, we used Bayesian Sparse Linear Mixed Model (BSLMM) to calculate the SNP expression weight of a gene's 1-Mb *cis* loci [17]. Let w denotes the weights. Z denotes the scores of gut microbiota. L denotes the SNP-correlation matrix. The association testing statistics between predicted gene expression and each taxon was calculated as $Z_{TWAS} = w'Z / (w'Lw)^{1/2}$. The imputed expression data can be regarded as a linear model of genotypes with weights based on the correlation between gene expression and SNPs in the training data, linkage disequilibrium (LD) among SNPs was considered [13]. Finally, the association between target traits and the expression level of genes was estimated by integrating analysis of mGWAS summary data with gene expression weights. The precomputed expression weights of tissues derived from the genotype-Tissue expression (GTEx) project were downloaded from FUSION websites (<http://gusevlab.org/projects/fusion/>). Specific in this study, we used

the sigmoid colon and transverse colon as reference panels. Following the recommendation in FUSION software [13], we generated the cleaned mGWAS summary statistics data by leverage LD reference panel for further analyses, and the mGWAS summary statistics have not been trimmed or thresholded before. The percentage of SNPs in the LD reference available in the FGFP mGWAS data was approximately 13.8% for each microbial trait. We implemented 2000 permutation tests for each FUSION analysis to reduce the inflation of by-chance QTL colocalization. In this study, the analytical permutation P value ($P_{\text{PERM.ANL}} < 0.05$) were considered to be significant.

TWAS fine mapping

Fine-mapping of causal gene sets (FOCUS) approach was performed for prioritizing genes with strong evidence for causality in TWAS analyses [18]. FOCUS integrates GWAS summary data and expression prediction weights estimated from the eQTL reference panel, considering the LD of all SNPs in the risk region, and finally estimates the probability (probability estimates of causality, PIP) of any given gene set to explain the TWAS signal [18] for each gene. The gene included in 90%-credible set is more likely to be causal than any other gene in the region. Consistently with TWAS analyses, the transverse colon and sigmoid colon were used as the reference panels in FOCUS analysis. The threshold for screening of mGWAS summary data was 1×10^{-5} [16].

Functional analyses

The gut microbiota related genes identified by TWAS ($P_{\text{PERM.ANL}} < 0.05$) were used for functional analyses by Functional Mapping and Annotation (FUMA) online platform [19]. P values were calculated by FUMA for each Gene Ontology (GO) term and pathway. The FDR P value < 0.05 was considered as significant.

Verification of gene and disease association

The literature mining was performed to show the lists of diseases related to the genes. The PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) was searched to identify whether the significant genes of each taxon identified by TWAS were the causal gene of the target diseases.

Results

TWAS results

In total, the TWAS of 157 microbial traits were performed by FUSION. In presence/absence (P/A-HB) phenotype, 1693 genes were identified by TWAS for overall 62 microbial traits (Additional file 1: Table S1, Additional file 2: Table S2, Additional file 3: Table S3), such as TOB2P1 for *Enterococcaceae* in sigmoid colon ($P_{\text{PERM.ANL}} = 1.94 \times 10^{-50}$), KCNIP3 for *Veillonellaceae*

in transverse colon ($P_{\text{PERM.ANL}} = 8.35 \times 10^{-33}$), WDR6 for *Coprococcus* in sigmoid colon ($P_{\text{PERM.ANL}} = 1.1 \times 10^{-16}$). Accordingly, 2247 genes were detected for 95 microbial traits in abundance (AB-RNT) phenotype, such as WDR6 for *Butyrivibrio* in sigmoid colon ($P_{\text{PERM.ANL}} = 1.24 \times 10^{-64}$), FBXO41 for *Clostridium* XIVa in transverse colon ($P_{\text{PERM.ANL}} = 1.47 \times 10^{-21}$), CENPE for *Veillonellaceae* in sigmoid colon ($P_{\text{PERM.ANL}} = 2.30 \times 10^{-17}$). Table 1 summarizes the top 20 significant genes associated with microbiota in two phenotypes, respectively.

We summarized overlapped candidate genes for different microbial traits (Fig. 1, Additional file 4: Table S4), such as NDUFV3 for *Lentisphaerae* (HB), *Bacteroidales* (HB), *Prevotella* (HB), an unclassified genus of order *Clostridiales* (RNT), an unclassified genus of family *Ruminococcaceae* (RNT), *Victivallis* (HB), *Bacteroides* (RNT), *Sporobacter* (RNT), an unclassified genus of phylum *Bacteroidetes* (HB), Chao diversity (RNT) and the number of genera observed (RNT); and SFTPD gene for *Rhodospirillaceae* (HB), *Alphaproteobacteria* (HB), an unclassified genus of phylum *Proteobacteria* (HB), *Rhodospirillales* (HB) and an unclassified genus of family *Rhodospirillaceae* (HB). Table 2 shows top 6 genes with the most repeats for microbial traits.

Fine mapping results

We performed fine mapping by FOCUS for 157 microbial traits with two reference panels, and finally found 11 genes included in 90%-credible sets, indicating the genes may causally associated with microbial traits (Table 3). Among them, 3 genes have been identified in TWAS analyses: HELLS for *Streptococcus* (RNT) (PIP=0.685) in sigmoid colon, HELLS for *Streptococcaceae* (RNT) (PIP=0.665) in sigmoid colon, ANO7 for *Erysipelotrichaceae* (RNT) (PIP=0.449) in sigmoid colon, and STAG3L4 for *Lachnospiraceae* (RNT) (PIP=0.171) in transverse colon.

Functional analyses results

The significant genes identified by TWAS for each microbial trait in the two tissues were subjected to functional analysis (Additional file 7: Table S7). Totally, we detected 94 GO terms in two phenotypes. For instance, GO_NUCLEOSIDE_DIPHOSPHATASE_ACTIVITY was significant for *Butyrivibrio* (RNT) (FDR $P = 1.30 \times 10^{-4}$), GO_CONDENSED_CHROMOSOME_CENTROMERIC_REGION was significantly associated with *Acidaminococcus* (HB) (FDR $P = 1.17 \times 10^{-3}$), GO_SPECTRIN_BINDING was detected to be correlated with *Burkholderiales* (RNT) (FDR $P = 1.69 \times 10^{-3}$), and GO_VACUOLE was associated with *Enterobacteriaceae* (RNT) (FDR $P = 2.84 \times 10^{-3}$).

Table 1 Top 20 candidate genes detected by TWAS in P/A and AB models

Gene	Tissue	Microbiota trait	Z	P
P/A-HB phenotype				
DNAJC9-AS1	Transverse colon	G_Ruminococcus	- 2.28	4.66×10^{-154}
CCDC36	Sigmoid colon	F_Enterococcaceae	- 2.22	6.46×10^{-130}
RP11-804H8.6	Sigmoid colon	F_Enterobacteriaceae	2.02	1.19×10^{-55}
TOB2P1	Sigmoid colon	F_Enterococcaceae	2.02	1.94×10^{-50}
ARHGAP1	Transverse colon	C_Gammaproteobacteria	1.96	4.85×10^{-44}
RP11-697N18.3	Transverse colon	F_Peptostreptococcaceae	2.54	3.91×10^{-33}
KCNIP3	Transverse colon	F_Veillonellaceae	1.97	8.35×10^{-33}
C3orf18	Sigmoid colon	C_Deltaproteobacteria	- 2.34	3.61×10^{-27}
C3orf18	Sigmoid colon	F_Enterobacteriaceae	- 2.07	5.68×10^{-22}
AC011330.5	Sigmoid colon	G_Clostridium_sensu_stricto	- 2.19	3.47×10^{-21}
RNF138P1	Sigmoid colon	G_Gemmiger	2.029	1.56×10^{-19}
ARIH2	Transverse colon	G_Coprococcus	2.57	3.39×10^{-18}
ELMO3	Transverse colon	G_Collinsella	- 2.33	1.02×10^{-16}
RP11-344N10.5	Sigmoid colon	G_Bifidobacterium	- 2.04	1.09×10^{-16}
WDR6	Sigmoid colon	G_Coprococcus	- 2.07	1.10×10^{-16}
CYP1A1	Transverse colon	G_Paraprevotella	2.30	2.60×10^{-15}
PROM2	Sigmoid colon	G_F_Coriobacteriaceae	2.65	1.74×10^{-13}
CYP1A1	Transverse colon	G_F_Porphyrimonadaceae	2.28	9.01×10^{-13}
FBXO41	Transverse colon	G_Lactococcus	- 2.44	4.30×10^{-12}
PROM2	Sigmoid colon	G_F_Rhodospirillaceae	2.07	3.46×10^{-11}
AB-RNT phenotype				
RP3-462E2.5	Transverse colon	G_Sporobacter	2.243	3.53×10^{-98}
WDR6	Sigmoid colon	G_Butyrvibrio	2.50	1.24×10^{-64}
ARIH2	Transverse colon	G_P_Proteobacteria	- 3.33	2.18×10^{-63}
TOB2P1	Sigmoid colon	G_Ruminococcus2	2.01	2.72×10^{-29}
IGKV6-21	Transverse colon	G_Collinsella	2.16	3.56×10^{-26}
C3orf18	Transverse colon	F_Enterobacteriaceae	- 2.77	3.09×10^{-24}
C3orf18	Sigmoid colon	C_Gammaproteobacteria	- 2.00	4.03×10^{-22}
FBXO41	Transverse colon	G_Clostridium_XIVa	- 2.60	1.47×10^{-21}
IGKV6-21	Transverse colon	G_P_Bacteroidetes	- 2.16	3.58×10^{-21}
RP11-10C24.3	Sigmoid colon	G_Sutterella	2.97	1.07×10^{-19}
C3orf18	Transverse colon	C_Gammaproteobacteria	- 2.14	7.08×10^{-19}
ZNF33A	Transverse colon	G_P_Bacteroidetes	2.50	8.09×10^{-19}
SLC33A1	Sigmoid colon	G_Sutterella	- 2.28	1.10×10^{-17}
DNAJB12	Transverse colon	P_Proteobacteria	2.59	1.19×10^{-17}
CENPE	Sigmoid colon	F_Veillonellaceae	2.20	2.30×10^{-17}
MUTYH	Transverse colon	G_Prevotella	- 2.39	2.74×10^{-17}
RP11-365H22.2	Transverse colon	O_Burkholderiales	2.08	3.75×10^{-16}
SIL1	Transverse colon	G_Streptococcus	2.31	1.10×10^{-15}
GINM1	Sigmoid colon	G_F_Lachnospiraceae	2.50	2.80×10^{-15}
RP11-365H22.2	Transverse colon	G_P_Firmicutes	1.97	2.26×10^{-14}

FUMA also identified 11 pathways related to microbial traits, such as KEGG_RENIN_ANGIOTENSIN_SYSTEM for *Anaerostipes* (RNT) (FDR $P=3.16 \times 10^{-2}$),

KEGG_PURINE_METABOLISM for *Veillonellaceae* (HB) (FDR $P=7.35 \times 10^{-3}$), KEGG_JAK_STAT_SIGNALING_PATHWAY for *Enterococcaceae* (RNT) (FDR

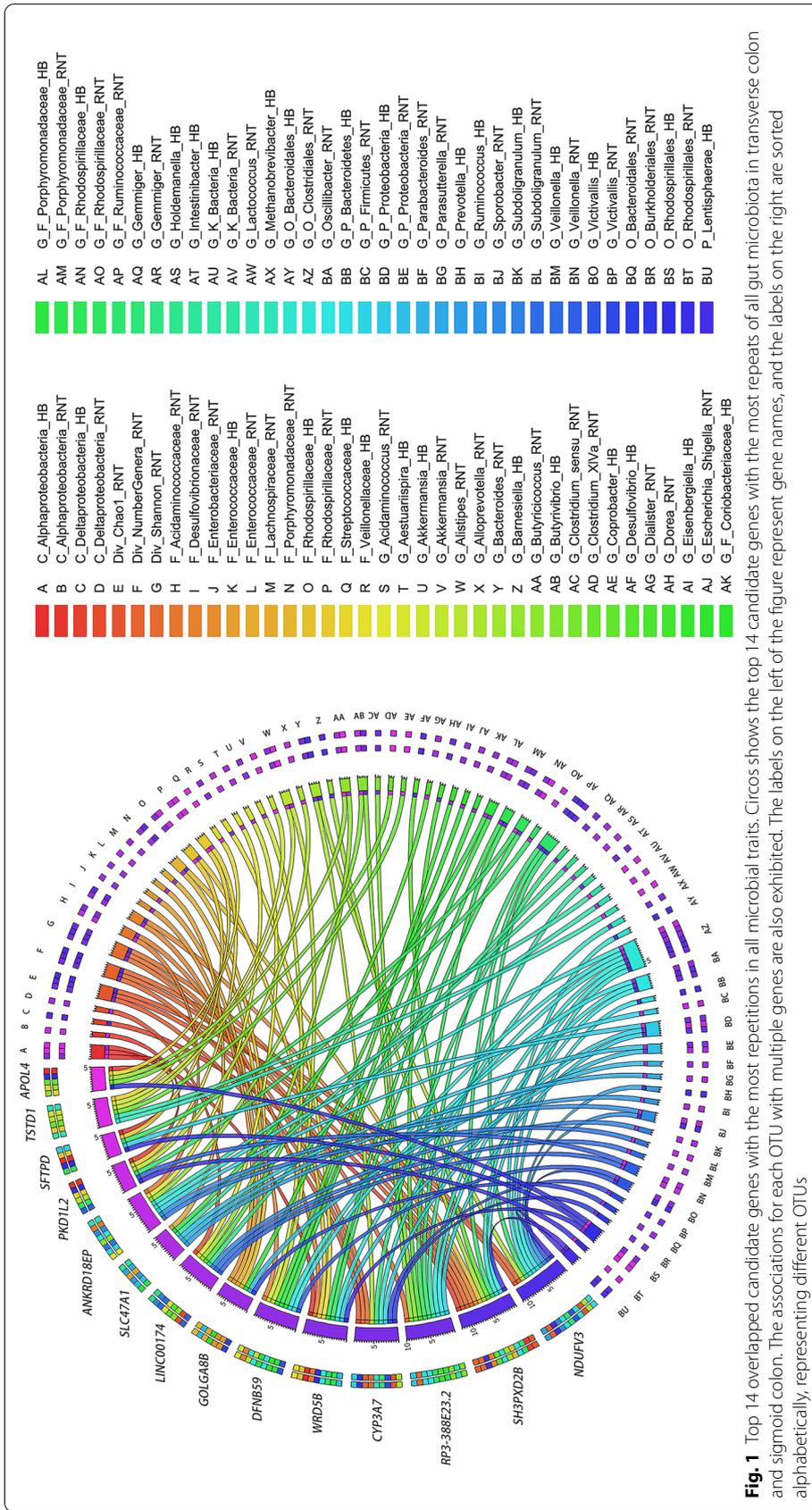


Fig. 1 Top 14 overlapped candidate genes with the most repetitions in all microbial traits. Circos shows the top 14 candidate genes with the most repeats of all gut microbiota in transverse colon and sigmoid colon. The associations for each OTU with multiple genes are also exhibited. The labels on the left of the figure represent gene names, and the labels on the right are sorted alphabetically, representing different OTUs

Table 2 Top 6 overlapped candidate genes for different microbial traits

Gene	Tissue	Microbial trait	Z	P	
NDUFV3	Sigmoid colon	P_Lentisphaerae_HB	3.61	1.35×10^{-3}	
	Sigmoid colon	Div_NumberGenera_RNT	3.52	1.58×10^{-3}	
	Sigmoid colon	G_O_Bacteroidales_HB	3.45	1.96×10^{-3}	
	Sigmoid colon	G_Prevotella_HB	3.25	1.99×10^{-3}	
	Sigmoid colon	G_O_Clostridiales_RNT	3.33	2.01×10^{-3}	
	Sigmoid colon	Div_Chao1_RNT	3.18	2.48×10^{-3}	
	Transverse colon	P_Lentisphaerae_HB	3.41	2.51×10^{-3}	
	Transverse colon	G_O_Clostridiales_RNT	3.20	3.19×10^{-3}	
	Sigmoid colon	G_F_Ruminococcaceae_RNT	3.35	3.65×10^{-3}	
	Sigmoid colon	G_Victivallis_HB	3.08	4.37×10^{-3}	
	Transverse colon	G_O_Bacteroidales_HB	2.98	4.64×10^{-3}	
	Sigmoid colon	G_Bacteroides_RNT	- 3.22	5.11×10^{-3}	
	Transverse colon	G_Bacteroides_RNT	- 3.30	6.08×10^{-3}	
	Sigmoid colon	G_Sporobacter_RNT	3.26	1.01×10^{-2}	
	Sigmoid colon	G_P_Bacteroidetes_HB	2.85	1.14×10^{-2}	
SH3PXD2B	Sigmoid colon	Div_Shannon_RNT	- 4.04	1.26×10^{-3}	
	Sigmoid colon	Div_Chao1_RNT	- 3.54	1.44×10^{-3}	
	Sigmoid colon	G_F_Ruminococcaceae_RNT	- 3.49	1.60×10^{-3}	
	Sigmoid colon	F_Desulfovibrionaceae_RNT	- 3.54	1.87×10^{-3}	
	Sigmoid colon	F_Porphyrionadaceae_RNT	- 4.02	2.04×10^{-3}	
	Sigmoid colon	Div_NumberGenera_RNT	- 3.46	2.58×10^{-3}	
	Sigmoid colon	G_Desulfovibrio_HB	- 3.42	2.64×10^{-3}	
	Sigmoid colon	C_Deltaproteobacteria_HB	- 3.16	3.33×10^{-3}	
	Sigmoid colon	G_O_Clostridiales_RNT	- 3.55	4.15×10^{-3}	
	Sigmoid colon	G_Barnesiella_HB	- 3.50	4.77×10^{-3}	
	Sigmoid colon	P_Lentisphaerae_HB	- 3.47	5.03×10^{-3}	
	Sigmoid colon	G_Oscillibacter_RNT	- 3.72	6.04×10^{-3}	
	RP3-388E23.2	Transverse colon	G_Butyriovibrio_HB	3.93	3.46×10^{-5}
		Transverse colon	Div_Shannon_RNT	3.43	4.13×10^{-4}
		Transverse colon	G_O_Clostridiales_RNT	2.70	1.33×10^{-3}
Transverse colon		G_Clostridium_sensu_RNT	2.71	2.73×10^{-3}	
Transverse colon		G_F_Ruminococcaceae_RNT	2.72	2.94×10^{-3}	
Sigmoid colon		G_F_Ruminococcaceae_RNT	2.61	5.84×10^{-3}	
Sigmoid colon		G_F_Porphyrionadaceae_RNT	2.56	7.77×10^{-3}	
Sigmoid colon		G_Dorea_RNT	2.06	1.04×10^{-2}	
Transverse colon		G_P_Proteobacteria_HB	2.43	1.21×10^{-2}	
Sigmoid colon		G_Intestinibacter_HB	2.08	1.98×10^{-2}	
CYP3A7	Transverse colon	G_Oscillibacter_RNT	2.22	2.44×10^{-2}	
	Transverse colon	G_Bacteroides_RNT	- 2.46	6.27×10^{-6}	
	Transverse colon	G_P_Proteobacteria_HB	2.28	7.96×10^{-6}	
	Transverse colon	G_Methanobrevibacter_HB	2.31	3.04×10^{-5}	
	Transverse colon	Div_Chao1_RNT	2.76	3.29×10^{-5}	
	Transverse colon	Div_NumberGenera_RNT	2.48	1.59×10^{-4}	
	Transverse colon	O_Burkholderiales_RNT	2.60	2.94×10^{-4}	
	Transverse colon	G_Victivallis_RNT	2.26	4.90×10^{-4}	
	Transverse colon	Div_Shannon_RNT	2.45	6.20×10^{-4}	
	Transverse colon	G_Gemmiger_HB	2.68	6.51×10^{-4}	
	Transverse colon	G_Methanobrevibacter_HB	2.19	9.41×10^{-4}	

Table 2 (continued)

Gene	Tissue	Microbial trait	Z	P
WDR5B	Sigmoid colon	F_Veillonellaceae_HB	- 3.20	4.99 × 10 ⁻⁴
	Transverse colon	G_F_Porphyrimonadaceae_RNT	3.31	2.00 × 10 ⁻³
	Sigmoid colon	G_F_Porphyrimonadaceae_RNT	3.35	2.05 × 10 ⁻³
	Sigmoid colon	O_Rhodospirillales_HB	3.20	3.45 × 10 ⁻³
	Sigmoid colon	G_O_Clostridiales_RNT	2.37	3.57 × 10 ⁻³
	Sigmoid colon	C_Alphaproteobacteria_HB	3.37	3.91 × 10 ⁻³
	Sigmoid colon	G_P_Proteobacteria_RNT	- 2.51	4.66 × 10 ⁻³
	Transverse colon	F_Acidaminococcaceae_RNT	- 2.49	4.75 × 10 ⁻³
	Sigmoid colon	F_Rhodospirillaceae_HB	2.97	4.80 × 10 ⁻³
	Sigmoid colon	G_F_Rhodospirillaceae_HB	2.76	6.18 × 10 ⁻³
DFNB59	Sigmoid colon	G_F_Porphyrimonadaceae_HB	- 3.67	7.08 × 10 ⁻⁵
	Sigmoid colon	G_Akkermansia_HB	- 2.64	6.56 × 10 ⁻⁴
	Sigmoid colon	F_Desulfovibrionaceae_RNT	- 3.30	8.33 × 10 ⁻⁴
	Sigmoid colon	G_Oscillibacter_RNT	- 3.87	8.78 × 10 ⁻⁴
	Sigmoid colon	G_Victivallis_HB	- 2.99	1.42 × 10 ⁻³
	Sigmoid colon	G_O_Clostridiales_RNT	- 3.13	1.97 × 10 ⁻³
	Sigmoid colon	G_F_Coriobacteriaceae_HB	- 2.99	2.54 × 10 ⁻³
	Sigmoid colon	G_Alistipes_RNT	- 2.85	2.91 × 10 ⁻³
	Sigmoid colon	G_Eisenbergiella_HB	- 2.12	3.39 × 10 ⁻³

Table 3 Potentially causal genes for microbial traits detected by FOCUS

Gene	Chrom	Microbial trait	Reference panel	PIP	Identified by TWAS
METTL15P1	3	G_Faecalitalea_RNT	Sigmoid colon	0.821	NO
COL5A1-AS1	9	G_Parasutterella_RNT	Sigmoid colon	0.801	NO
RP1-257A7.4	6	G_Veillonella_RNT	Sigmoid colon	0.714	NO
HELLS	10	G_Streptococcus_RNT	Sigmoid colon	0.685	YES
HELLS	10	F_Streptococcaceae_RNT	Sigmoid colon	0.665	YES
FBXO27	19	G_Aestuariuspira_RNT	Sigmoid colon	0.555	NO
NIPSNAP1	22	G_Clostridium_sensu_RNT	Sigmoid colon	0.537	NO
ANO7	2	F_Erysipelotrichaceae_RNT	Sigmoid colon	0.449	YES
FRRS1L	9	G_P_Firmicutes_RNT	Transverse colon	0.826	NO
RP11-1277A3.2	5	G_Intestinibacter_RNT	Transverse colon	0.114	NO
STAG3L4	7	G_Lachnospiraceae_RNT	Transverse colon	0.171	YES
CPNE8	12	G_F_Porphyrimonadaceae_RNT	Transverse colon	0.201	NO

The integral fine mapping results are shown in Additional file 5, 6: Table S5–S6

$P=2.60 \times 10^{-2}$). Table 4 shows the top 10 gene ontology terms and KEGG pathways of the significant genes.

Association between candidate genes and diseases

The selected top genes in Tables 1 and 2 were searched on PubMed website to explore the possible relationship

with diseases, and 12 genes were found to be associated with 12 diseases (Table 5). For instance, HELLS for *Streptococcus* in sigmoid colon was related to colorectal cancer [20], and SFTPD for an unclassified genus of *Proteobacteria* in transverse colon was detected to be related to atherosclerosis [21]. Specifically, although

Table 4 Top 10 significant GO and KEGG pathways for microbial traits

GeneSet	Microbial trait	FDR P
GO term		
GO_NUCLEOSIDE_DIPHOSPHATASE_ACTIVITY	G_Butyrvibrio_RNT	1.30×10^{-4}
GO_CONDENSED_CHROMOSOME_CENTROMERIC_REGION	G_Acidaminococcus_HB	1.17×10^{-3}
GO_KINETOCHORE	G_Acidaminococcus_HB	1.17×10^{-3}
GO_CHROMOSOMAL_REGION	G_Acidaminococcus_HB	1.39×10^{-3}
GO_SPECTRIN_BINDING	O_Burkholderiales_RNT	1.69×10^{-3}
GO_CHROMOSOME_CENTROMERIC_REGION	G_Acidaminococcus_HB	2.55×10^{-3}
GO_VACUOLE	F_Enterobacteriaceae_RNT	2.84×10^{-3}
GO_OXIDOREDUCTASE_ACTIVITY_ACTIVATING_ON_PAIRED_DONORS_WITH_INCORPORATION_OR_REDUCTION_OF_MOLECULAR_OXYGEN_REDUCED_FLAVIN_OR_FLAVOPROTEIN_AS_ONE_DONOR_AND_INCORPORATION_OF_ONE_ATOM_OF_OXYGEN	G_unclassified_F_Porphyrimonadaceae_HB	3.62×10^{-3}
GO_STEROID_HYDROXYLASE_ACTIVITY	G_unclassified_F_Porphyrimonadaceae_HB	3.62×10^{-3}
GO_CONDENSED_CHROMOSOME	G_unclassified_F_Porphyrimonadaceae_HB	3.73×10^{-3}
KEGG pathway		
KEGG_RETINOL_METABOLISM	G_unclassified_F_Porphyrimonadaceae_HB	3.35×10^{-3}
KEGG_METABOLISM_OF_XENOBIOTICS_BY_CYTOCHROME_P450	G_unclassified_F_Porphyrimonadaceae_HB	3.35×10^{-3}
KEGG_PURINE_METABOLISM	F_Veillonellaceae_HB	7.35×10^{-3}
KEGG_METABOLISM_OF_XENOBIOTICS_BY_CYTOCHROME_P450	Div_Shannon_RNT	7.36×10^{-3}
KEGG_FC_GAMMA_R_MEDIATED_PHAGOCYTOSIS	O_Selenomonadales_RNT	1.28×10^{-2}
KEGG_NEUROACTIVE_LIGAND_RECEPTOR_INTERACTION	F_Desulfovibrionaceae_RNT	1.48×10^{-2}
KEGG_PYRIMIDINE_METABOLISM	F_Veillonellaceae_HB	2.07×10^{-2}
KEGG_JAK_STAT_SIGNALING_PATHWAY	F_Enterococcaceae_RNT	2.60×10^{-2}
KEGG_LYSOSOME	F_Enterobacteriaceae_RNT	2.81×10^{-2}
KEGG_RENIN_ANGIOTENSIN_SYSTEM	G_Anaerostipes_RNT	3.16×10^{-2}

The integral functional analyses results are shown in Additional file 7: Table S7

Table 5 The list of candidate genes associated with diseases

Gene	Microbial trait	Reference panel	Gene-related disease	Reference
NDUFV3	Div_Chao1_RNT	Sigmoid colon	Down syndrome	PMID: 26848775
ARIH2	G_Coprococcus_HB	Transverse colon	Parkinson's disease	PMID: 31284572
ZNF33A	G_P_Bacteroidetes_RNT	Transverse colon	Major depressive disorder	PMID: 32554045
ARHGAP1	C_Gammaproteobacteria_HB	Transverse colon	Ischemic heart disease	PMID: 31664016
CYP3A7	Div_Chao1_RNT	Transverse colon	Bilirubin metabolic disorder	PMID: 32499339
SFTPD	G_P_Proteobacteria_RNT	Transverse colon	Atherosclerosis	PMID: 26748346
LSG1	G_Streptococcus_RNT	Sigmoid colon	Attention-deficit hyperactivity disorder	PMID: 30738099
SH3PXD2B	F_Porphyrimonadaceae_RNT	Sigmoid colon	Osteoporosis	PMID: 30962481
FUT2	G_Bifidobacterium_HB	Transverse colon	Crohn's disease	PMID: 31260595
PKD1L2	G_Alloprevotella_RNT	Transverse colon	Colorectal cancer	PMID: 27605020
HELLS	G_Streptococcus_RNT	Sigmoid colon	Colorectal cancer	PMID: 32063710
ANO7	F_Erysipelotrichaceae_RNT	Sigmoid colon	Prostate cancer	PMID: 30157291

not included in the top genes, FUT2 for *Bifidobacterium* was suggested to be the causal gene for Crohn's disease (CD) in previous study [22].

Discussion

Host genes have been shown to be closely related to the ecosystem of the gut microbiota. Previous studies have

detected multiple candidate genes associated with specific taxa [23–25]. Recent studies indicated that non-coding regulatory regions play an important role in influencing human complex traits. The gut microbiota was once suggested as a complex trait of the host affected by mbQTL [8], so we speculate that the host can influence the composition of the gut microbiota and the abundance of specific groups by regulating gene expression. In this study, TWAS was performed to prioritize candidate genes affecting gut microbiota at gene expression level by integrating GWAS summary data and specific pre-computed tissue expression profile. Finally, we identified numbers of genes and pathways related to microbial traits, and some of the genes have been reported to be associated with specific diseases by previous studies.

TWAS and fine mapping both prioritized several candidate genes for gut microbiota, such as HELLS for *Streptococcus* in sigmoid colon, ANO7 for *Erysipelotrichaceae* in sigmoid colon. We attempted to explore the relationship between gut microbiota candidate genes and diseases. HELLS encodes lymphoid specific, which participates in the establishment and maintenance of DNA methylation with chromatin remodeling through its ATPase activity [20]. HELLS expression was proved to be significantly associated with the colorectal cancer progression and a higher pathological grade [20]. Aberrant bands of the HELLS was observed in seven colorectal cancers by polymerase chain reaction-based single strand conformation polymorphism assay [26]. *Streptococcus* has been identified as colorectal cancer candidate pathogens in previous researches [27, 28]. ANO7 has been found to play a central role in prostate cancer progression, and its elevated expression correlates with disease severity and outcome [29]. Notably, the abundance of *Erysipelotrichaceae* was observed to be increased in prostate cancer patients [30]. In the treatment of prostate cancer by androgen axis targeted therapy, men receiving the treatment showed a significant decrease in the abundance of sequencing reads assigned to *Erysipelotrichaceae* [31]. In gut microbiota of mice, the abundance of *Erysipelotrichaceae* was also different between cancer bearing mice and healthy mice [32].

FUT2 was detected to be associated with *Bifidobacterium* in transverse colon in TWAS. FUT2 gene encodes α -1, 2-fucosyltransferase for the expression of ABH blood group antigens on mucosal surfaces, and determines the ability to secrete blood group antigens into gastrointestinal secretions. Individuals who have homozygous non-coding variants in FUT2 are nonsecretors, and ABH antigens are not expressed in mucosal secretions and surfaces, generally called as sese [33, 34]. Accordingly, secretory type was expressed as SeSe and Sese [34].

The alterations of FUT2 genotype resulted in a significant shift of microbial composition, that is, the gardening effect of FUT2 polymorphism on phylogenetic composition of the gut microbiota [34]. Present studies consistently show the genome-wide significant association between FUT2 non-secretor allele and CD in various races [22, 35]. It is suggested that FUT2 gene loss-of-function allele homozygotes change the gut microbiota of CD patients [36–39]. FUT2 polymorphism may also partly contribute to CD susceptibility by shaping community composition and structure of microbiota [36, 37]. Previous studies showed genus *Bifidobacterium* had higher diversity, richness and abundance in secretors compared with non-secretors [40, 41]. Moreover, increased genus *Bifidobacterium* is related to successful clinical outcome or remission of therapy in CD [42]. Further studies are warranted to identify the interactions between FUT2, *Bifidobacterium* and CD.

TWAS also identified SFTPD as a candidate gene for an unclassified genus of *Proteobacteria* in transverse colon. SFTPD encodes surfactant protein D, which is an important host defense lectin. It aggregates and enhances phagocytosis of microbes and dying host cells [43]. SFTPD is mainly expressed in lung, but also distributes in gallbladder and gut, and could shape intestinal microbial ecosystem [43]. Some potential evidence has carried out the link between SFTPD and phylum *Proteobacteria*. Nexoe et al., found a strong positive correlation between inflammatory activity and expression of SFTPD in the intestinal epithelium from Inflammatory Bowel Disease (IBD) patients [44], while the increase of *Proteobacteria* is one of the most consistent observations in IBD individuals [45].

SFTPD was reported exacerbating the development of atherosclerosis in previous literatures [21, 46–48]. In recent decades, bacterial infections and chronic inflammation have become possible causes of cardiovascular disease. Atherosclerosis is a chronic inflammatory process driven by lipids in the walls of the great arteries [49]. SFTPD has been proved to play a predominant role in pro-inflammatory [50, 51]. According to previous studies, the genus of *Proteobacteria* were involved in the formation of atherosclerosis. For instance, *Proteus vulgaris* was found to be present in the plaques and intestines of the same individual [52], *Proteus mirabilis* can interact with atherosclerosis plaques in human coronary arteries via specific molecular to exacerbate the progression of disease [53]. In addition, the abundance of *Proteus* in the blood of cardiovascular disease patients was observed to be increased compared with healthy individuals [52]. In mouse disease models, the reduction of phylum

Proteobacteria abundance can exert a therapeutic effect on atherosclerosis [54]. Since the SFTPD is related to the abundance of bacteria from phylum *Proteobacteria* based on our findings, we hypothesized that the microbiota could affect susceptibility to atherosclerosis by genetic regulation.

KEGG_RENIN_ANGIOTENSIN_SYSTEM was detected to be associated with *Anaerostipes* in functional analysis. In a recent study, the fewer abundance of *Anaerostipes* was observed in primary aldosteronism patients than healthy individuals [55]. Bier et al. have confirmed that high salt diet could lead to decreased the abundance of taxa from the *Anaerostipes* genus [56]. Moreover, *Anaerostipes* was found to be correlated with higher estimated glomerular filtration rate in the overall population [57].

To the best of our knowledge, we conducted the first large-scale comprehensive sigmoid colon and transverse colon tissue-specific TWAS for gut microbiota, and performed fine mapping based on TWAS for further confirmation. The candidate genes for gut microbiota were further explored for the link between various taxa and diseases. Our study also has three potential limitations. First, only individuals of European ancestry from Germany and Belgium were included in the analysis, so the results cannot be generalized to other ethnic groups. Second, the information about diet and drug use of individuals is lack so that we can't rule out the effects of diet and medication on the composition of gut microbiota. Third, it should be marked that the purpose of this study is to screen and prioritize candidate genes for gut microbiota, the results should be interpreted with caution. At present, research based on the interaction of genes and gut microbiota still needs more extensive exploration, further functional studies should be performed to confirm our findings and elucidate the mechanisms which genes act on gut microbiota.

Conclusions

To be conclude, we performed TWAS analyses and identified multiple candidate genes and pathways of gut microbiota. We found that some candidate genes may also involve in the susceptibility of diseases, and attempted to provide clues for revealing the influence of genetic factors on gut microbiota for the occurrence and development of diseases. Our findings may provide new insight into the influence of genetic factors on the composition of gut microbiota, in addition to suggesting the potential role of gut microbiota in the mechanism of genetic factors contributing to disease susceptibility. Further studies are needed to demonstrate specific biological mechanisms in the future.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13099-021-00474-w>.

Additional file 1: Table S1. The number of candidate genes for each microbial traits identified by TWAS.

Additional file 2: Table S2. TWAS results for gut microbiota in sigmoid colon.

Additional file 3: Table S3. TWAS results for gut microbiota in transverse colon.

Additional file 4: Table S4. Top 14 overlapped candidate gene for different microbial traits.

Additional file 5: Table S5. Fine mapping results for gut microbiota in sigmoid colon.

Additional file 6: Table S6. Fine mapping results for gut microbiota in transverse colon.

Additional file 7: Table S7. Functional analyses results for microbial traits.

Acknowledgements

Not applicable.

Authors' contributions

CP and FZ conceived and designed the study; CP and YN wrote the manuscript; SC collected the data and carried out the statistical analyses; YJ, YW, CL, HZ, JC, JZ, ZZ, XY and PM made preparations for the manuscript at first. All authors reviewed and approved the final manuscript.

Funding

This study was supported by the National Natural Scientific Foundation of China (81673112, 81703177), the Key projects of international cooperation among governments in scientific and technological innovation (2016YFE0119100), the Natural Science Basic Research Plan in Shaanxi Province of China (2017JZ024), and the Fundamental Research Funds for the Central Universities.

Availability of data and materials

Raw 16S data used in the original GWAS study are available at the European Genome/Phenome Archive under accession no. EGAS00001004420. The microbiome GWAS summary data support the findings of this study are available online at the University of Bristol data repository with the identifier <https://doi.org/10.5523/bris.22bqn399f9i432q56gt3wfhzlc>. The precomputed expression weights of tissues derived from the genotype-Tissue expression (GTEx) project were downloaded from FUSION websites <http://gusevlab.org/projects/fusion/>. The TWAS results of this study have been deposited in the Figshare repository at the following <http://dx.doi.org/10.6084/m9.figshare.14387162>.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors gave their consent for publications.

Competing interests

The authors state that they have no competing interests.

Received: 7 August 2021 Accepted: 7 December 2021

Published online: 18 December 2021

References

- Schoeler M, Caesar R. Dietary lipids, gut microbiota and lipid metabolism. *Rev Endocr Metab Disord*. 2019;20(4):461–72.
- Hagan T, Cortese M, Roupael N, Boudreau C, Linde C, Maddur MS, et al. Antibiotics-driven gut microbiome perturbation alters immunity to vaccines in humans. *Cell*. 2019;178(6):1313–28e13.
- Plaza-Díaz J, Álvarez-Mercado AI, Ruiz-Marín CM, Reina-Pérez I, Pérez-Alonso AJ, Sánchez-Andujar MB, et al. Association of breast and gut microbiota dysbiosis and the risk of breast cancer: a case–control clinical study. *BMC Cancer*. 2019;19(1):495.
- Pulikkan J, Mazumder A, Grace T. Role of the gut microbiome in autism spectrum disorders. *Adv Exp Med Biol*. 2019;1118:253–69.
- Fu J, Bonder MJ, Cenit MC, Tigchelaar EF, Maatman A, Dekens JA, et al. The gut microbiome contributes to a substantial proportion of the variation in blood lipids. *Circ Res*. 2015;117(9):817–24.
- Zhernakova A, Kurilshikov A, Bonder MJ, Tigchelaar EF, Schirmer M, Vatanen T, et al. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. *Science*. 2016;352(6285):565–9.
- Lim MY, You HJ, Yoon HS, Kwon B, Lee JY, Lee S, et al. The effect of heritability and host genetics on the gut microbiota and metabolic syndrome. *Gut*. 2017;66(6):1031–8.
- Benson AK, Kelly SA, Legge R, Ma F, Low SJ, Kim J, et al. Individuality in gut microbiota composition is a complex polygenic trait shaped by multiple environmental and host genetic factors. *Proc Natl Acad Sci USA*. 2010;107(44):18933–8.
- Bonder MJ, Kurilshikov A, Tigchelaar EF, Mujagic Z, Imhann F, Vila AV, et al. The effect of host genetics on the gut microbiome. *Nat Genet*. 2016;48(11):1407–12.
- Wainberg M, Sinnott-Armstrong N, Mancuso N, Barbeira AN, Knowles DA, Golan D, et al. Opportunities and challenges for transcriptome-wide association studies. *Nat Genet*. 2019;51(4):592–9.
- Westra HJ, Franke L. From genome to function by studying eQTLs. *Biochim Biophys Acta*. 2014;1842(10):1896–902.
- Bosse Y. Genome-wide expression quantitative trait loci analysis in asthma. *Curr Opin Allergy Clin Immunol*. 2013;13(5):487–94.
- Gusev A, Ko A, Shi H, Bhatia G, Chung W, Penninx BW, et al. Integrative approaches for large-scale transcriptome-wide association studies. *Nat Genet*. 2016;48(3):245–52.
- Liao C, Laporte AD, Spiegelman D, Akcimen F, Joobor R, Dion PA, et al. Transcriptome-wide association study of attention deficit hyperactivity disorder identifies associated genes and phenotypes. *Nat Commun*. 2019;10(1):4450.
- Zhong J, Jermusyk A, Wu L, Hoskins JW, Collins I, Mocchi E, et al. A transcriptome-wide association study identifies novel candidate susceptibility genes for pancreatic cancer. *J Natl Cancer Inst*. 2020;112(10):1003–12.
- Hughes DA, Bacigalupe R, Wang J, Rühlemann MC, Tito RY, Falony G, et al. Genome-wide associations of human gut microbiome variation and implications for causal inference analyses. *Nat Microbiol*. 2020;5(9):1079–87.
- Zhou X, Carbonetto P, Stephens M. Polygenic modeling with bayesian sparse linear mixed models. *PLoS Genet*. 2013;9(2):e1003264.
- Mancuso N, Freund MK, Johnson R, Shi H, Kichaev G, Gusev A, et al. Probabilistic fine-mapping of transcriptome-wide association studies. *Nat Genet*. 2019;51(4):675–82.
- Watanabe K, Taskesen E, van Bochoven A, Posthuma D. Functional mapping and annotation of genetic associations with FUMA. *Nat Commun*. 2017;8(1):1826.
- Liu X, Hou X, Zhou Y, Li Q, Kong F, Yan S, et al. Downregulation of the helicase lymphoid-specific (HELLS) gene impairs cell proliferation and induces cell cycle arrest in colorectal cancer cells. *Onco Targets Ther*. 2019;12:10153–63.
- Sorensen GL, Bladbjerg EM, Steffensen R, Tan Q, Madsen J, Drivsholm T, et al. Association between the surfactant protein D (SFTPD) gene and subclinical carotid artery atherosclerosis. *Atherosclerosis*. 2016;246:7–12.
- Ye BD, Kim BM, Jung S, Lee HS, Hong M, Kim K, et al. Association of FUT2 and ABO with Crohn's disease in Koreans. *J Gastroenterol Hepatol*. 2020;35(1):104–9.
- Lamas B, Richard ML, Leducq V, Pham HP, Michel ML, Da Costa G, et al. CARD9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands. *Nat Med*. 2016;22(6):598–605.
- Ruan JW, Statt S, Huang CT, Tsai YT, Kuo CC, Chan HL, et al. Dual-specificity phosphatase 6 deficiency regulates gut microbiome and transcriptome response against diet-induced obesity in mice. *Nat Microbiol*. 2016;2:16220.
- Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S, et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science*. 2010;328(5975):228–31.
- Choi YJ, Yoo NJ, Lee SH. Mutation of HELLS, a chromatin remodeling gene, gastric and colorectal cancers. *Pathol Oncol Res*. 2015;21(3):851–2.
- Gagnière J, Raisch J, Veziat J, Barnich N, Bonnet R, Buc E, et al. Gut microbiota imbalance and colorectal cancer. *World J Gastroenterol*. 2016;22(2):501–18.
- Cheng Y, Ling Z, Li L. The intestinal microbiota and colorectal cancer. *Front Immunol*. 2020;11:615056.
- Kaikkonen E, Rantapero T, Zhang Q, Taimen P, Laitinen V, Kallajoki M, et al. ANO7 is associated with aggressive prostate cancer. *Int J Cancer*. 2018;143(10):2479–87.
- Kalinen S, Kallonen T, Gunell M, Ettala O, Jambor I, Knaapila J, et al. Gut microbiota signatures associate with prostate cancer risk. *medRxiv*. 2021;80:134.
- Sfanas KS, Markowski MC, Peiffer LB, Ernst SE, White JR, Pienta KJ, et al. Compositional differences in gastrointestinal microbiota in prostate cancer patients treated with androgen axis-targeted therapies. *Prostate Cancer Prostatic Dis*. 2018;21(4):539–48.
- Marco A, De Velasco KS, Yurie Kura, Eri Banno, Naomi Ando, Noriko Sako, Kazuhiro Yoshikawa, Kazuto Nishio, Hirotsugu Uemura, editor Abstract 3340: Prostate cancer alters gut microbiota in mice. AACR Annual Meeting; 2020; Philadelphia.
- Ferrer-Admetlla A, Sikora M, Laayouni H, Esteve A, Roubinet F, Blancher A, et al. A natural history of FUT2 polymorphism in humans. *Mol Biol Evol*. 2009;26(9):1993–2003.
- Tong M, McHardy I, Ruegger P, Goudarzi M, Kashyap PC, Haritunians T, et al. Reprogramming of gut microbiome energy metabolism by the FUT2 Crohn's disease risk polymorphism. *ISME J*. 2014;8(11):2193–206.
- McGovern DP, Jones MR, Taylor KD, Marcante K, Yan X, Dubinsky M, et al. Fucosyltransferase 2 (FUT2) non-secretor status is associated with Crohn's disease. *Hum Mol Genet*. 2010;19(17):3468–76.
- Rausch P, Rehman A, Künzel S, Häslér R, Ott SJ, Schreiber S, et al. Colonic mucosa-associated microbiota is influenced by an interaction of Crohn disease and FUT2 (Secretor) genotype. *Proc Natl Acad Sci USA*. 2011;108(47):19030–5.
- Wacklin P, Tuimala J, Nikkilä J, Sebastian T, Mäkiuokko H, Alakulppi N, et al. Faecal microbiota composition in adults is associated with the FUT2 gene determining the secretor status. *PLoS ONE*. 2014;9(4):e94863.
- Rao S, Shi M, Han X, Lam MHB, Chien WT, Zhou K, et al. Genome-wide copy number variation-, validation- and screening study implicates a new copy number polymorphism associated with suicide attempts in major depressive disorder. *Gene*. 2020;755:144901.
- Rausch P, Künzel S, Suwandi A, Grassl GA, Rosenstiel P, Baines JF. Multi-generational influences of the Fut2 gene on the dynamics of the gut microbiota in mice. *Front Microbiol*. 2017;8:991.
- Wacklin P, Mäkiuokko H, Alakulppi N, Nikkilä J, Tenkanen H, Räsänen J, et al. Secretor genotype (FUT2 gene) is strongly associated with the composition of Bifidobacteria in the human intestine. *PLoS ONE*. 2011;6(5):e20113.
- Kumbhare SV, Kumar H, Chowdhury SP, Dhotre DP, Endo A, Mättö J, et al. A cross-sectional comparative study of gut bacterial community of Indian and Finnish children. *Sci Rep*. 2017;7(1):10555.
- Neurath MF. Host-microbiota interactions in inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol*. 2020;17(2):76–7.
- Holmskov U, Thiel S, Jensenius JC. Collections and ficolins: humoral lectins of the innate immune defense. *Annu Rev Immunol*. 2003;21:547–78.
- Nexoe AB, Pilecki B, Von Huth S, Husby S, Pedersen AA, Detlefsen S, et al. Colonic epithelial surfactant protein D expression correlates with inflammation in clinical colonic inflammatory bowel disease. *Inflamm Bowel Dis*. 2019;25(8):1349–56.
- Matsuoka K, Kanai T. The gut microbiota and inflammatory bowel disease. *Semin Immunopathol*. 2015;37(1):47–55.

46. Hirano Y, Choi A, Tsuruta M, Jaw JE, Oh Y, Ngan D, et al. Surfactant protein-D deficiency suppresses systemic inflammation and reduces atherosclerosis in ApoE knockout mice. *Cardiovasc Res.* 2017;113(10):1208–18.
47. Barrow AD, Palarasah Y, Bugatti M, Holehouse AS, Byers DE, Holtzman MJ, et al. OSCAR is a receptor for surfactant protein D that activates TNF- α release from human CCR2+ inflammatory monocytes. *J Immunol.* 2015;194(7):3317–26.
48. Hu F, Zhong Q, Gong J, Qin Y, Cui L, Yuan H. Serum surfactant protein D is associated with atherosclerosis of the carotid artery in patients on maintenance hemodialysis. *Clin Lab.* 2016;62(1–2):97–104.
49. Chistiakov DA, Melnichenko AA, Myasoedova VA, Grechko AV, Orekhov AN. Role of lipids and intraplaque hypoxia in the formation of neovascularization in atherosclerosis. *Ann Med.* 2017;49(8):661–77.
50. Sorensen GL. Surfactant protein d in respiratory and non-respiratory diseases. *Front Med (Lausanne).* 2018;5:18.
51. Colmorton KB, Nexoe AB, Sorensen GL. The dual role of surfactant protein-D in vascular inflammation and development of cardiovascular disease. *Front Immunol.* 2019;10:2264.
52. Klionsky DJ, Abdel-Aziz AK, Abdelfatah S, Abdellatif M, Abdoli A, Abel S, et al. Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition)(1). *Autophagy.* 2021;17(1):1–382.
53. Xue Y, Li Q, Park CG, Klena JD, Anisimov AP, Sun Z, et al. Proteus mirabilis targets atherosclerosis plaques in human coronary arteries via DC-SIGN (CD209). *Front Immunol.* 2020;11:579010.
54. Li F, Zhang T, He Y, Gu W, Yang X, Zhao R, et al. Inflammation inhibition and gut microbiota regulation by TSG to combat atherosclerosis in ApoE(–/–) mice. *J Ethnopharmacol.* 2020;247:112232.
55. Liu Y, Jiang Q, Liu Z, Shen S, Ai J, Zhu Y, et al. Alteration of gut microbiota relates to metabolic disorders in primary aldosteronism patients. *Front Endocrinol (Lausanne).* 2021;12:667951.
56. Bier A, Braun T, Khasbab R, Di Segni A, Grossman E, Haberman Y, et al. A high salt diet modulates the gut microbiota and short chain fatty acids production in a salt-sensitive hypertension rat model. *Nutrients.* 2018;10(9).
57. Mazidi M, Shekoohi N, Covic A, Mikhailidis DP, Banach M. Adverse impact of *Desulfovibrio* spp. and beneficial role of *Anaerostipes* spp. on renal function: insights from a mendelian randomization analysis. *Nutrients.* 2020;12(8).

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

