

The Involvement of Gut Microbiota in the Development of Glioblastoma

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CITATION

Mingming X, Ting X. et al. The Involvement of Gut Microbiota in the Development of Glioblastoma. *Psycho-Oncologie*.

ARTICLE INFO

Received:
Accepted:
Available online:

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Abstract: Objective The involvement of gut microbiota (GM) in the initiation, progression, and treatment of cancer has garnered heightened scholarly interest. Consequently, this study employed Mendelian randomization (MR) to examine the causal relationship between GM and glioblastoma (GBM). Methods The genome-wide association study (GWAS) summary data from the MiBioGen Consortium were utilized as exposure variables, while the GBM GWAS summary data were sourced from the FinnGen consortium, specifically versions R10 (comprising 253 cases and 314,319 controls) and R11 (comprising 378 cases and 345,118 controls). The primary analytical approach employed was the inverse variance weighted method, which was further complemented by MR-Egger regression, the weighted median method, the simple model, and the weighted model. Heterogeneity was evaluated using Cochran's Q test, and pleiotropy was assessed through the MR-Egger intercept and MR-PRESSO methods. To ensure robustness, a leave-one-out sensitivity analysis was conducted to identify and exclude anomalous results. Results In the R10 version of the FinnGen consortium, we identified eight taxa with causal relationships to GBM. In the subsequent R11 version, which utilized a larger sample size, we identified nine taxa with significant associations. Through comparative analysis, it was determined that Melainabacteria, Gastranaerophilales, and Victivallaceae were consistently significant across both versions, with consistent effect directions. Specifically, Melainabacteria and Gastranaerophilales were associated with a significant reduction in GBM risk, whereas Victivallaceae was associated with a significant increase in GBM risk. The six additional gut microbiota taxa identified as significant in the R11 version alone may reflect previously undetected weak associations, likely revealed due to the increased sample size. Conclusions This study elucidated the potential causal relationship between GM and GBM using two-sample MR and confirmed the robustness of the findings across various iterations of the FinnGen consortium. The results offer novel insights for the development of clinical intervention strategies for patients with GBM.

Keywords: Gut microbiota; Glioblastoma; Bidirectional mendelian randomization; Causality

Glioblastoma (GBM) represents the most prevalent and aggressive form of glioma, constituting approximately 45% of all glioma cases ^[1]. The condition is characterized by a high recurrence rate and a poor prognosis following treatment, thereby exerting a substantial burden on both families and society ^[2]. Consequently, it is imperative to elucidate the biological pathogenic factors contributing to GBM and to implement preventive strategies. Nevertheless, the specific risk factors associated with GBM remain largely unidentified. Aside from infrequent genetic predispositions and exposure to radiation, no additional risk factors have been definitively linked to the development of GBM ^[3].

The gut microbiota (GM) constitutes an extensive microbial ecosystem within the human gastrointestinal tract, which has been implicated in the pathogenesis of various human diseases ^[4] and holds significant promise for clinical applications ^[5]. Scientific investigations have elucidated a sophisticated bidirectional communication network among the brain, the gut, and the GM, referred to as the “microbiota-gut-brain axis” ^[6]. Further research into these intricate mechanisms has suggested that the GM may play a role in the onset and progression of brain-related disorders, such as GBM, through pathways involving neurotransmitters, immune modulation, and metabolic processes, among others [7, 8].

Traditional observational epidemiological research methods often suffer from a lack of sufficient randomized controlled trial data and are susceptible to confounding factors and reverse causality. Consequently, establishing a definitive causal relationship and direction between GM and GBM remains challenging. Mendelian randomization (MR) is an analytical approach designed to evaluate causal relationships between risk factors and diseases. By employing single nucleotide polymorphisms (SNPs) that are closely associated with exposure factors as instrumental variables (IVs), MR can effectively mitigate biases arising from confounding factors or reverse causality [9, 10]. This method is regarded as a robust tool for epidemiological statistical analysis ^[11]. Previous studies have utilized MR to investigate the causal relationships between GM and cerebrovascular diseases ^[12], as well as brain tumors ^[13]. Nonetheless, there is a paucity of systematic MR research specifically addressing GBM, a highly malignant brain glioma with a poor prognosis.

In this study, we intend to utilize the bidirectional two-sample MR approach to investigate the potential association between GM and GBM. Our objective is to elucidate the causal relationship between the risk of occurrence of GM and GBM from a genetic standpoint, uncover the underlying biological mechanisms, and consequently offer novel insights and strategies for the future prevention and treatment of GBM.

1. Materials and Methods

Data Sources The aggregated statistical data pertaining to GM were sourced from a genome-wide association studies (GWAS) meta-analysis conducted by the

MiBioGen Alliance in Europe. This comprehensive study encompassed 24 cohorts across 11 countries, involving a total of 18,340 participants, predominantly of European descent. After excluding GM classification units with unknown designations, the analysis focused on 196 taxonomic groups, comprising 9 phyla, 16 classes, 20 orders, 35 families, and 131 genera. Additionally, the aggregated statistical data concerning GBM were derived from the R10 version of the FinnGen Alliance, which included 314,446 individuals of European ancestry (253 cases and 314,193 controls). To ensure the robustness and reproducibility of the study's findings, the GBM dataset from the FinnGen Alliance's R11 version (378 cases and 345,118 controls) was utilized for MR validation analysis under identical conditions. All GWAS datasets employed in this study have received ethical approval from the relevant review boards. As this research exclusively utilized aggregated statistical data from these studies, no additional ethical approval was necessary.

2. Research Design and Statistical Analysis

To ensure the reliability of the inferred causal relationships, this study implemented rigorous quality control measures, including heterogeneity, multiplicity, and sensitivity analyses, among others. Furthermore, the MR analysis was conducted in strict adherence to the three fundamental assumptions of MR^[14]: the association assumption, which requires a strong correlation between IVs and the exposure factor; the independence assumption, which necessitates the independence of IVs from confounding factors; and the exclusivity assumption, which stipulates that the effect of IVs on the outcome is mediated solely through the exposure factor. The overall design of this study is illustrated in Figure 1.

Selection of Instrumental Variables The process of selecting instrumental variables is primarily guided by the three core assumptions of MR: (1) SNPs are chosen based on a stringent association with the instrumental variable, defined by a p-value threshold of less than 1e-05, while employing parameters of $R^2 = 0.001$ and a 10,000 Kb window to eliminate SNPs exhibiting linkage disequilibrium^[15]; (2) The strength of the instrumental variables is assessed using the F-statistic, calculated as $\text{Beta}^2/\text{SE}^2$. An F-statistic less than 10 signifies a weak instrumental variable, necessitating its exclusion from the analysis^[16]; (3) SNPs that are palindromic with intermediate allele frequencies, such as those with A/T or G/C alleles, are removed; (4) The online platform LDlink is utilized to identify and eliminate SNPs that are associated with potential confounding variables related to GBM and are directly linked to the outcome (<https://ldlink.nci.nih.gov/?tab=ldtrait>).

Mendelian Randomization Analysis In this study, the inverse variance weighted (IVW) method was employed as the primary approach for MR analysis^[17]. This method computes a weighted average based on the inverse of the variance. Under the conditions where all IVs are valid and there is no hetero-

geneity or pleiotropy, the IVW method provides the most reliable estimate of the causal relationship between GM and GBM. A statistically significant result from the IVW method ($P < 0.05$) is interpreted as evidence of a causal relationship between GM and GBM. Additionally, we utilized MR-Egger regression, the weighted median method (WM), the weighted mode (WMe), and the simple mode (SM) as supplementary analytical approaches. Each of these methods assessed the causal relationship between GM and GBM using P values, with the Odds Ratio (OR) indicating the effect size. The MR-Egger regression is applicable when more than 50% of the IVs are subject to horizontal pleiotropy^[18]. The WM method can yield consistent estimates if at least half of the weights are derived from valid IVs^[19]. Similarly, the WMe approach provides more accurate estimates when at least 50% of the IVs are valid^[20].

Heterogeneity Test To assess statistical heterogeneity among SNPs, the Cochran's Q test is applied within the framework of the IVW model. $P < 0.05$ indicates the presence of statistical heterogeneity among the SNPs, warranting the adoption of a random effects model. This model provides unbiased estimates by accounting for potential horizontal pleiotropy and aims to achieve balance in such scenarios. Conversely, $P > 0.05$ suggests the absence of statistical heterogeneity among the SNPs.

Horizontal Pleiotropy The presence of horizontal pleiotropy is evaluated using both the MR-Egger intercept and MR-PRESSO methods. $P < 0.05$ for either the MR-Egger intercept or MR-PRESSO indicates the presence of horizontal pleiotropy, which may introduce bias into the MR results. Furthermore, MR-PRESSO is employed to identify and remove outlier SNPs, thereby mitigating the impact of horizontal pleiotropy on the MR findings^[21].

Sensitivity Analysis The influence of individual SNPs on the outcomes of the IVW analysis was assessed through the leave-one-out approach. In this method, each SNP was sequentially excluded to compute the meta-effect of the remaining SNPs, thereby evaluating its impact on the overall causal effect^[22].

Reverse MR To determine whether the causal relationship between GM and GBM is influenced by reverse causation, the same dataset and conditional parameters were employed. Specifically, the bacterial groups identified as positive in the forward MR analysis were utilized as the outcome variable, while GBM served as the exposure variable in the reverse MR analysis.

All statistical analyses in this study were conducted using R software (version 4.3.1), employing R packages such as "GenomicSEM" (version 0.0.5), "TwoSampleMR" (version 0.5.11), and "MR-PRESSO" (version 1.0) for MR analysis.

3. Results

3.1 The Causal Impact of Gut Microbiota on Glioblastoma

3.1.1 Causal Effect of Gut Microbiota on Glioblastoma Utilizing the selec-

tion criteria for IVs, a total of 72 independent SNPs from eight bacterial categories were identified for MR studies. These SNPs were robust and not influenced by weak instrumental variables. Comprehensive details are provided in Table 1 of the supplementary material. The IVW analysis revealed causal relationships between eight GMs and GBM, as illustrated in Figure 2. Additional information is available in Table 2. Specifically, at the family level, the presence of Victivallaceae (id.2255) (OR = 1.925, 95% CI : 1.225 - 3.026, P = 0.005) and Bacteroidaceae (Bacteroides id.917) (OR = 3.439, 95% CI: 1.120 - 10.554, P = 0.031) was positively associated with an increased risk of GBM. At the genus level, Bacteroides (id.918) (OR = 3.439, 95% CI: 1.120 - 10.554, P = 0.031), Olsenella (id.8222) (OR = 1.640, 95% CI: 1.017 - 2.645, P = 0.042), and the Eubacterium brachy group (id.11296) (OR = 2.059, 95% CI: 1.200 - 3.533, P = 0.009) were also positively correlated with the risk of GBM. In addition, at the phylum level, Cyanobacteria (Cyanobacteria id.1500) (OR = 0.442, 95% CI : 0.208 - 0.939, P = 0.034) and at the class level, Melainabacteria (Melainabacteria id.1589) (OR = 0.454, 95% CI : 0.241 - 0.855, P = 0.013), and at the order level, Gastranaerophilales (Gastranaerophilales id.1591) (OR = 0.433, 95% CI : 0.223 - 0.838, P = 0.013) were negatively correlated with the risk of GBM. The scatter plot of the MR analysis results of GM and GBM is shown in Figure 3.

3.1.2 Heterogeneity, Horizontal Multiplicity, and Sensitivity Analysis The Cochran's Q test, MR-Egger intercept, and MR-PRESSO analysis applied to the IVW model yielded P values exceeding 0.05, suggesting a lack of heterogeneity and horizontal multiplicity (Table 1). Furthermore, the "leave-one-out" sensitivity analysis (Figure 4) did not reveal any specific SNPs exerting a significant influence on the results, thereby reinforcing the reliability and robustness of our Mendelian Randomization findings.

3.2 Causal Impact of GBM on GM

In the reverse MR analysis, the IVW results indicated that all P-values (PIVW) exceeded 0.05. This suggests the absence of a reverse causal relationship between GBM and the eight candidate GMs identified through positive MR. Furthermore, the Cochran's Q test, the intercept of the MR-Egger regression, and the P-value of MR-PRESSO were all greater than 0.05 (Table 2), demonstrating that our MR analysis results regarding the causal relationship between GBM and GM were not influenced by heterogeneity or horizontal pleiotropy. The leave-one-out sensitivity test did not identify any SNPs that significantly impacted the results, thereby reinforcing the robustness of our final MR findings (Figure 5).

3.3 R11 Validation Analysis

Given the limited availability of GWAS datasets for GBM, the summary statistics pertaining to GBM from the R11 release of the FinnGen consortium were utilized for the internal MR validation analysis to assess the causal impact of GM on GBM. The IVW analysis revealed a statistically significant association

between nine bacterial taxa and GBM. Specifically, the Betaproteobacteria class (id.2867) (OR = 2.947, 95% CI : 1.142 - 2.549, P = 0.035), the Victivallaceae family (id.2255) (OR = 1.706, 95% CI : 1.142 - 2.549, P = 0.009), the genus *Escherichia Shigella* (id.3504) (OR = 2.534, 95% CI : 1.149 - 5.586, P = 0.021), and the genus *Barnesiella* (id.2867) (OR = 3.205, 95% CI : 1.309 - 7.845, P = 0.011) were identified as risk factors for GBM. Conversely, the Melainabacteria class (id.1589) (OR = 0.482, 95% CI : 0.287 - 0.817, P = 0.007), the Gastranaerophilales order (id.1591) (OR = 0.511, 95% CI : 0.293 - 0.888, P = 0.017), the genus *Coprococcus3* (id.11303) (OR = 0.255, 95% CI : 0.091 - 0.072, P = 0.011), the genus *Flavonifractor* (id.2059), and the genus *Propionibacterium* (OR = 0.423, 95% CI : 0.191 - 0.936, P = 0.034) were identified as protective factors against GBM (Figure 6). The heterogeneity and horizontal pleiotropy test analysis results showed that the P values were all greater than 0.05, indicating the absence of heterogeneity and horizontal pleiotropy.

Discussion

In this bidirectional Mendelian randomization study, we utilized the R10 and R11 GWAS datasets from the FinnGen Consortium to identify eight and nine gut microbiota taxa that are causally associated with GBM and GM, respectively. Notably, three taxonomic groups, including Melanobacteriaceae and Anaerobiales, demonstrated consistent effects across both dataset versions (OR : 0.442 – 0.511, P < 0.05), thereby reinforcing their potential involvement in the pathogenesis of GBM. The identification of additional taxonomic groups in the larger R11 cohort, such as β -Proteobacteria (OR = 2.947, 95% CI : 1.142 – 2.549, P = 0.035), may be attributed to the increased statistical power resulting from the expanded sample size, which included an additional 125 cases and 30,799 controls.

GBM represents the most aggressive form of primary brain tumor, and currently, no definitive cure exists for this condition^[23]. The gut microbiota is integral to human growth and development, metabolism, and immune regulation. Dysbiosis of the gut microbiota can influence the progression of numerous diseases^[24]. Understanding the specific relationships between particular microbiota and diseases is essential for developing targeted prevention and treatment strategies. A study investigating the relationship between male HIV-1 infection and gut microbiota revealed that individuals who progressed to AIDS within 5-10 years post-infection exhibited significantly higher levels of Enterobacteriaceae bacteria compared to a control group that was neither infected nor had received long-term antiretroviral therapy. Additionally, MR analysis suggested that Enterobacteriaceae bacteria might increase susceptibility to allergic rhinitis^[25] and thyroid cancer^[26, 27]. Conversely, an MR study on diabetic nephropathy identified Enterobacteriaceae bacteria as a protective factor^[28]. These ostensibly contradictory research findings further underscore the intricate and multifaceted roles of the gut microbiota, which are readily influenced by the host's physiological conditions, disease

types, and environmental factors, thereby exhibiting varying functions in different contexts. To date, the expression of food-derived Enterobacteriaceae in GBM patients, as well as its association with GBM susceptibility and severity, remains inadequately understood. Our study identified food-derived Enterobacteriaceae as significant components of the microbiota in both Mendelian randomization analysis groups, with consistent effect directions indicating an increased risk of GBM. Future research will concentrate on in-depth investigations to elucidate the mechanisms underlying these interactions and aim to develop prevention and treatment strategies targeting the Enterobacteriaceae microbiota.

Moreover, both the MR analysis and the repeated MR analysis have identified the Melanobacteria class and the Anaerobiales order in the stomach as protective factors against GBM. Contrary to our findings, previous studies have reported an increased abundance of the Melanobacteria class in patients with certain neurodegenerative, gastrointestinal, hepatic, and respiratory diseases^[29], suggesting its potential role in promoting disease onset and progression. Our study is the first to demonstrate the protective effect of Melanobacteria on glioblastoma using the MR method, thereby highlighting a novel association between gut microbiota and brain tumor risk. Although no prior research has directly associated Melanobacteria with glioblastoma, our results align with emerging evidence on the gut-brain axis and the involvement of gut microbiota in cancer development^[7]. Some studies have proposed that Melanobacteria may influence GBM risk indirectly through metabolites such as lactic acid^[30] and hydrogen gas^[31]; however, this remains speculative and lacks direct empirical support. The mechanism may involve lactate-driven tumor metabolic reprogramming, hydrogen gas-mediated anti-inflammatory effects, or metabolic interactions with other microbiota^[32, 33]. Future studies should combine multi-omics techniques and experimental models to verify their biological significance, which may open up new avenues for the prevention and treatment of glioblastoma.

In the context of gastric anaerobic bacteria, which are pivotal for indole production, prior research has suggested their involvement in cancer suppression via their metabolites, such as indole-3-acetic acid and short-chain fatty acids^[34]. Indole-3-acetic acid may facilitate the development of immune cells by activating the aryl hydrocarbon receptor (AHR)^[35, 36], thereby establishing a basis for anti-tumor activity. Short-chain fatty acids, particularly butyric acid, can enhance the polarization of anti-inflammatory macrophages (M2 type) to pro-inflammatory macrophages (M1 type) by inhibiting histone deacetylase (HDAC) activity, thus augmenting the anti-tumor immune response^[37]. Additionally, short-chain fatty acids can activate G protein-coupled receptors (GPCRs, such as GPR43^[38] and GPR109A^[39]), inhibit the nuclear factor kappa-B (NF- κ B) signaling pathway^[40], and decrease the release of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor α (TNF- α), thereby mitigating the inflammatory response within the tumor microenvironment^[40]. Collectively, our findings corroborate these earlier studies, suggesting that this microbial group may exert

a protective effect against the development of GBM. Our MR findings enhance the possibility of causality with the consistency of existing literature, and also highlight the necessity of further mechanism studies, such as comprehensive metagenomics and metabolomics analyses.

The primary strength of this study lies in its incorporation of an “internal validation” mechanism within the experimental design, which substantially enhances the stability of the assessment outcomes. Furthermore, the rigorous selection of IVs, the application of five MR research methods, and the implementation of a standardized quality control process collectively ensure the reliability of the MR assessment results. However, the study is not without limitations. Firstly, the systematic MR analysis conducted on two overlapping cohorts revealed discrepancies, with certain bacterial species being either added or omitted. This suggests that the conclusions derived from the MR analysis may not always be consistent. Specifically, for newly identified bacteria, we hypothesize that the increased sample size may have facilitated the detection of weak associations. Conversely, the omission of certain bacteria could be attributed to a reduction in false positives following the sample size increase or the introduction of changes in data updates. It is widely recognized that the primary distinction between datasets from different time periods within the Finnish database is the variation in sample size. This observation suggests that an increase in sample size tends to yield MR results that more accurately reflect the true situation. However, it also necessitates caution regarding potential new challenges that may arise with larger sample sizes, such as population stratification and confounding factors. Consequently, our primary focus is on bacterial groups that overlap and show significant associations with GBM. Future research will involve functional or cohort-based experiments to validate these causal relationships. Additionally, demographic factors, dietary habits, and medication use can influence the composition of the GM. These variables typically display diversity, individual variability, and low heritability, which can diminish the statistical power and reliability of the findings. Furthermore, the current GM sample size is limited and predominantly comprises individuals of European ancestry. While this may help mitigate the impact of external factors, it also implies that the findings may not be directly generalizable to individuals of other racial backgrounds. Therefore, further studies involving more participants from different racial backgrounds are needed to verify the universality of the research results in different races. Finally, it is necessary to introduce multi-omics data to explore the biological mechanisms of the interaction between GM and GBM.

In conclusion, this study utilized gut microbiome GWAS data from the MiBioGen consortium as the exposure variable and performed MR analyses using the aggregated statistics from the R10 and R11 versions of the GBM data from the FinnGen consortium. The findings revealed that 8 and 9 bacterial taxa exhibited a causal relationship with GBM. Notably, the Micrococcaceae order, the Anaerobiales class, and the Food Microbiota family demonstrated significant

correlations in both exploratory and confirmatory MR analyses, suggesting a robust causal association with GBM. It is important to highlight that the 6 bacterial taxa newly identified in the R11 version may represent weak associations, potentially attributed to the increased sample size, and their underlying mechanisms in relation to GBM warrant further investigation. While the expanded sample size enhanced statistical power, it may have also introduced additional confounding variables. Consequently, future research should integrate multi-omics data and functional experiments to validate these findings.

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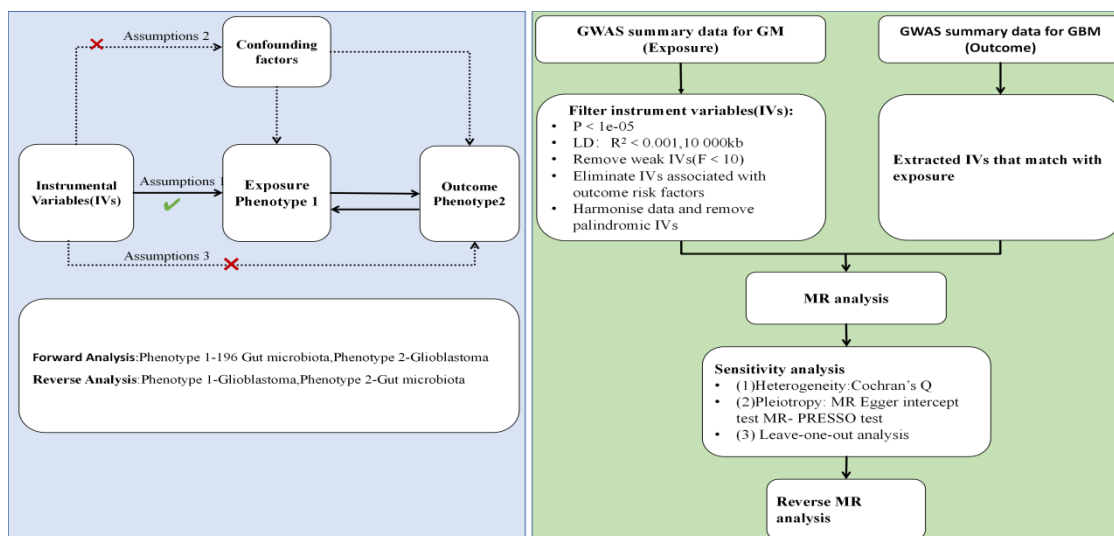
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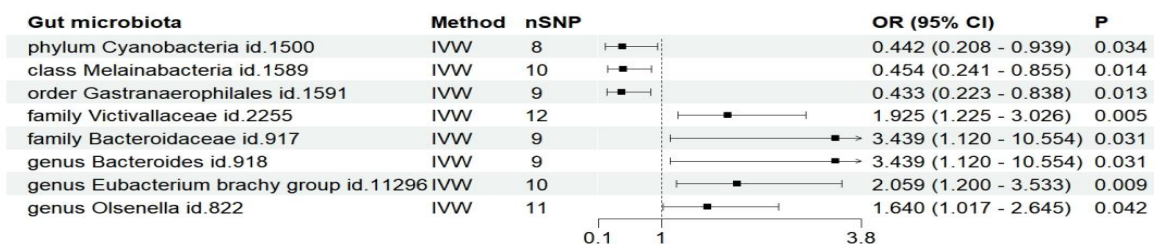
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Figure 1. General Design Drawing



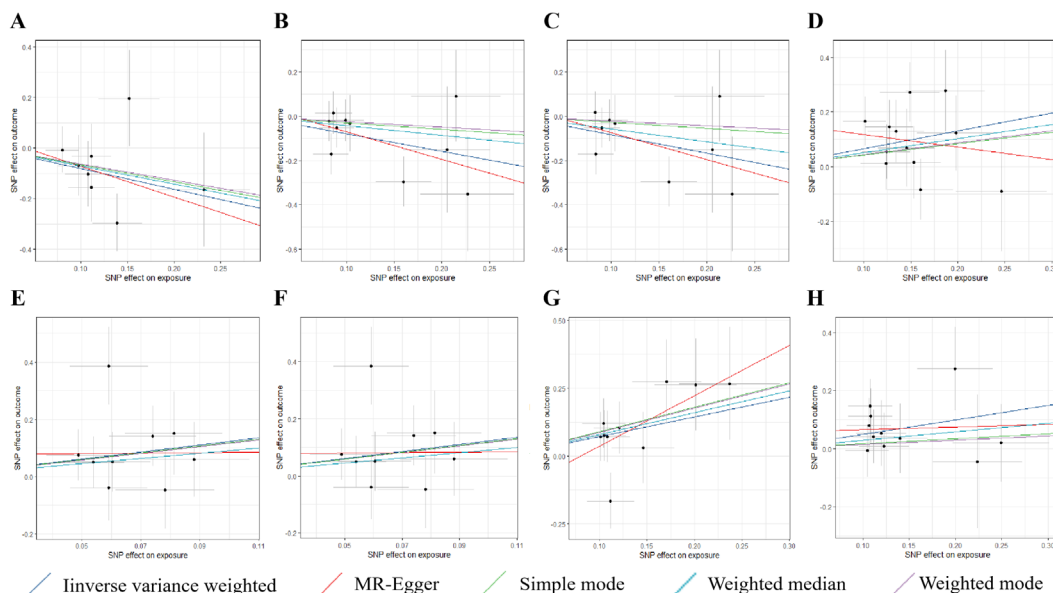
Overview of current MR analysis and assumptions. MR: Mendelian randomization; GWAS: Genome-wide association study; GM: Gut microbiota; GBM: glioblastoma; F: F-statistic.

Figure 2. Forest plot of the causal relationship between GM and GBM based on IVW



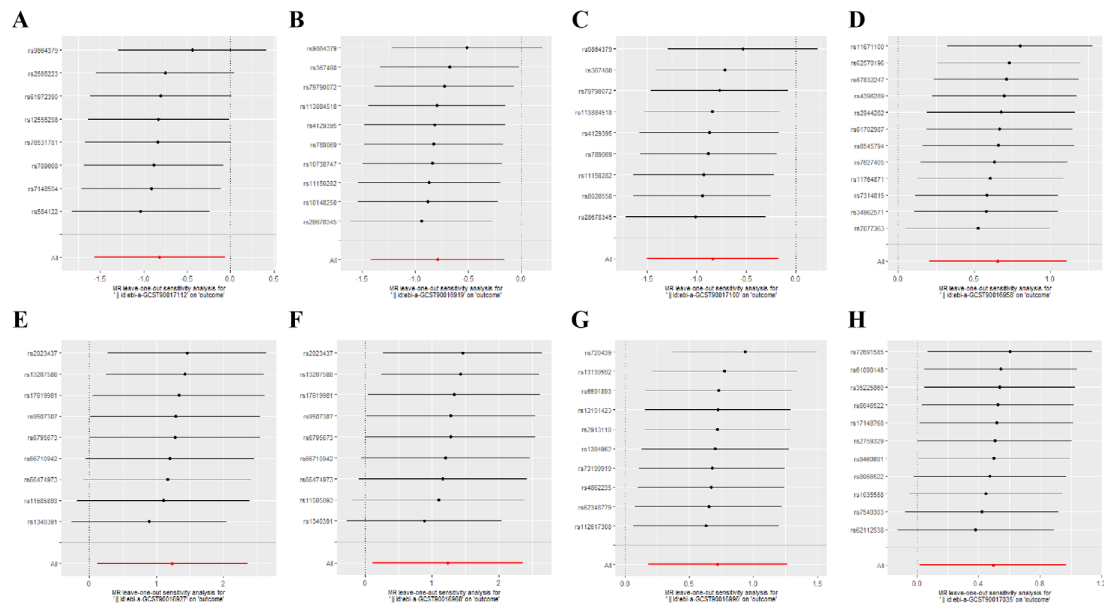
IVW: Inverse variance weighted; SNP: single-nucleotide polymorphisms; SE: standard error; F: F-statistic.

Figure 3. Scatter plot of association between GM and GBM



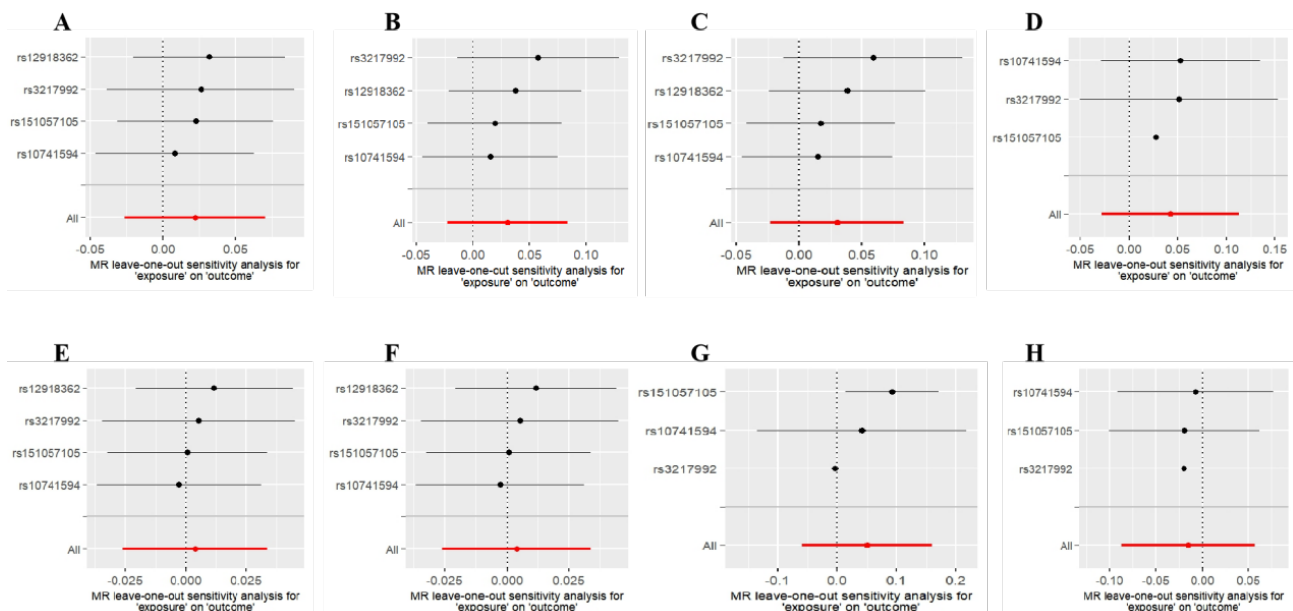
Each black dot represents a SNP, represented by the SNP estimate for exposure (x-axis) and the SNP estimate for parental outcome (y-axis). The slope of each line represents the possible causal relationship for each method. A: phylum Cyanobacteria id.1500. B: class Melainabacteria id.1589. C: order Gastranaerophilales id.1591. D: family Victivallaceae id.2255. E: family Bacteroidaceae id.917. F: genus Bacteroides id.918. G: genus Eubacterium brachy group id.11296. H: genus Olsenella id.822.

Figure 4. Leave-one-out plot of genes predicted to have significant causal relationships between GM and GBM.



A: phylum Cyanobacteria id.1500. B: class Melainabacteria id.1589. C: order Gastranaerophilales id.1591. D: family Victivallaceae id.2255. E: family Bacteroidaceae id.917. F: genus Bacteroides id.918. G: genus Eubacterium brachy group id.11296. H: genus Olsenella id.822.

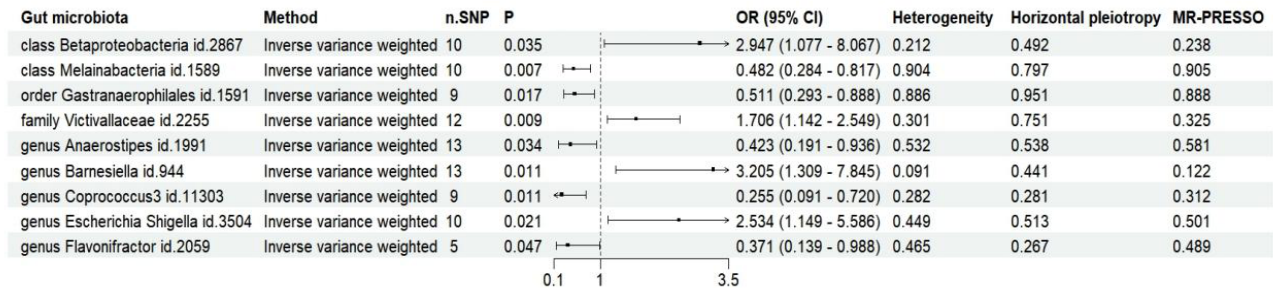
Figure 5. Leave-one-out results for reverse MR.



A: phylum Cyanobacteria id.1500. B: class Melainabacteria id.1589. C: order Gastranaerophilales id.1591. D: family Victivallaceae id.2255. E: family Bacteroidaceae id.917. F: genus Bacteroides id.918. G: genus Eubacterium brachy group id.11296. H: genus Olsenella id.822.

group id.11296. H: genus Olsenella id.822.

Figure 6. Causal analysis results of GM and GBM (FinnGen R11)



SNP: single-nucleotide polymorphisms; CI: Confidence interval.

Table 1. MR heterogeneity and horizontal pleiotropy results

Gut microbiota	Cochran's Q		MR-Egger		MR-PRESSO
	IVW				
	Q	P	Intercept	P	P
phylum Cyanobacteria id.1500	6.306	0.505	0.049	0.776	0.479
class Melainabacteria id.1589	7.141	0.622	0.053	0.635	0.585
order Gastranaerophilales id.1591	6.914	0.546	0.047	0.700	0.531
family Victivallaceae id.2255	10.727	0.466	0.164	0.325	0.535
family Bacteroidaceae id.917	7.987	0.435	0.076	0.718	0.51
genus Bacteroides id.918	7.987	0.435	0.076	0.718	0.518
genus Eubacterium brachy group id.11296	7.859	0.548	0.057	0.614	0.593
genus Olsenella id.822	4.780	0.905	-0.148	0.319	0.893

IVW:Inverse variance weighted

Table 2. Main results of reverse MR analysis

MR							Heterogeneity	Pleiotropy
Gut microbiota	Method	nSNP	P	OR	or_lci95	or_uci95	P	P
phylum Cyanobacteria id.1500	IVW	4	0.370	1.022	0.974	1.073	0.638	0.402
class Melainabacteria id.1589	IVW	4	0.264	1.031	0.977	1.087	0.478	0.722
order Gastranaerophilales id.1591	IVW	4	0.267	1.031	0.977	1.087	0.409	0.720
family Victivallaceae id.2255	IVW	3	0.234	1.044	0.973	1.119	0.708	0.559
family Bacteroidaceae id.917	IVW	4	0.805	1.004	0.974	1.034	0.583	0.369
genus Bacteroides id.918	IVW	4	0.805	1.004	0.974	1.034	0.583	0.369
genus Eubacterium brachy group id.11296	IVW	3	0.372	1.051	0.942	1.172	0.084	0.286
genus OIsenella id.822	IVW	3	0.682	0.985	0.917	1.059	0.933	0.823

IVW:Inverse variance weighted