

肠道微生物群和口腔扁平苔藓之间的因果关系：来自孟德尔随机化研究的见解

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摘要

背景与目的: 口腔扁平苔藓(Oral lichen planus, OLP)是一种口腔黏膜慢性炎症性疾病。先前的研究表明, 肠道微生物群在调节宿主免疫系统和炎症反应中具有重要作用, 并与多种慢性炎症性疾病密切相关。然而, 肠道菌群与OLP之间的因果关系尚未明确。本研究利用孟德尔随机化(MR)探索GM与OLP的因果关系, 为潜在的发病机制和治疗策略提供新的视角。**方法:** 本研究利用双样本(MR)方法探讨肠道菌群与OLP风险之间的潜在因果关系。肠道菌群遗传数据来源于MiBioGen联盟的全基因组关联研究(GWAS), 包括18,340名欧洲血统参与者, 涵盖119个属水平的菌群分类。OLP的GWAS数据来自FinnGen生物库(795例OLP患者和499,553名对照)。采用逆方差加权(IVW)、MR-Egger、加权中位数、简单模式和加权模式等多种方法, 通过计算比值比(OR)和置信区间(CI)评估因果关系, 并使用MR-Egger截距检验、Cochran's Q检验和留一法分析进行敏感性分析以确保结果的稳健性。**结果:** IVW方法显示, Subdoligranulum (OR = 0.548, 95% CI: 0.321~0.937, $p = 0.028$)、Family XIII UCG001 (OR = 0.583, 95% CI: 0.346~0.982, $p = 0.043$)、Prevotella7 (OR = 0.766, 95% CI: 0.589~0.995, $p = 0.046$)和Intestinibacter (OR = 0.616, 95% CI: 0.407~0.933, $p = 0.022$)与OLP风险降低相关, 而Ruminococcaceae UCG009 (OR = 1.459, 95% CI: 1.037~2.054, $p = 0.030$)与OLP风险增加相关。敏感性分析未发现显著的异质性或多效性($p > 0.05$), 留一法分析表明结果稳健。**结论:** 本研究通过孟德尔随机化分析首次揭示了肠道菌群与OLP风险之间的潜在因果关系。结果表明, Subdoligranulum、Family XIII UCG001、Prevotella7和Intestinibacter可能具有保护作用, 而Ruminococcaceae UCG009则与OLP风险增加相关。

关键词

口腔扁平苔藓, 肠道菌群, 孟德尔随机化

The Causal Relationship between Gut Microbiota and Oral Lichen Planus: Insights from Mendelian Randomization Studies

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Abstract

Background and Objectives: Oral lichen planus (OLP) is a chronic inflammatory disease of the oral mucosa. Previous studies have indicated that the gut microbiota plays a crucial role in regulating the host immune system and inflammatory responses, and is closely associated with various chronic inflammatory diseases. However, the causal relationship between the gut microbiota and OLP remains unclear. This study utilized Mendelian randomization (MR) to explore the causal relationship between the gut microbiota (GM) and OLP, providing new insights into potential pathogenesis and therapeutic strategies. **Methods:** This study employed a two-sample MR approach to investigate the potential causal relationship between the gut microbiota and OLP risk. The gut microbiota genetic data were sourced from the MiBioGen consortium's genome-wide association study (GWAS), which included 18,340 participants of European ancestry and covered 119 genera-level microbial taxa. The GWAS data for OLP came from the FinnGen biobank (795 OLP patients and 499,553 controls). Various methods, including inverse variance weighting (IVW), MR-Egger, weighted median, simple mode, and weighted mode, were applied to estimate causal relationships by calculating odds ratios (OR) and confidence intervals (CI). Sensitivity analyses were conducted using MR-Egger intercept test, Cochran's Q test, and leave-one-out analysis to ensure the robustness of the results. **Results:** The IVW method revealed that *Subdoligranulum* (OR = 0.548, 95% CI: 0.321~0.937, $p = 0.028$), *Family XIII UCG001* (OR = 0.583, 95% CI: 0.346~0.982, $p = 0.043$), *Prevotella7* (OR = 0.766, 95% CI: 0.589~0.995, $p = 0.046$), and *Intestinibacter* (OR = 0.616, 95% CI: 0.407~0.933, $p = 0.022$) were associated with a decreased risk of OLP, while *Ruminococcaceae UCG009* (OR = 1.459, 95% CI: 1.037~2.054, $p = 0.030$) was associated with an increased risk of OLP. Sensitivity analysis did not reveal significant heterogeneity or pleiotropy ($p > 0.05$), and the leave-one-out analysis indicated robust results. **Conclusion:** This study, through Mendelian randomization analysis, is the first to reveal a potential causal relationship between the gut microbiota and OLP risk. The findings suggest that *Subdoligranulum*, *Family XIII UCG001*, *Prevotella7*, and *Intestinibacter* may have a protective effect, while *Ruminococcaceae UCG009* is associated with an increased risk of OLP.

Keywords

Oral Lichen Planus, Gut Microbiota, Mendelian Randomization

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1. 引言

口腔扁平苔藓(Oral lichen planus, OLP)是一种常见的口腔黏膜慢性炎症性疾病, 主要影响 30~50 岁的人

群。全球患病率为 1.01% [1] 女性患病率高于男性[2]。约 2.28% 的 OLP 患者可发生恶变[3]。世界卫生组织(WHO)已将口腔扁平苔藓列为口腔潜在恶性疾病(OPMD) [4]。临床上, OLP 表现为多种症状, 包括口腔烧灼感和疼痛, 常伴有长期糜烂病变。尽管有药物、激光、手术、光动力疗法等多种治疗方法, 但目前尚无根治 OLP 的方法[5]。OLP 的病因尚不明确, 多种因素与其发病和进展相关, 包括微循环障碍、遗传易感性、免疫和内分泌异常以及心理应激[6] [7]。微生物在 OLP 的持续炎症和复发中起着至关重要的作用。健康的口腔菌群与免疫系统保持高度协调的动态平衡, 当免疫系统功能失调时, 这种平衡会被打破, 影响菌群的组成和功能。对 OLP 患者唾液的研究表明, 与健康人相比, OLP 患者唾液中细菌的数量和多样性均显著降低[8]。在 OLP 患者中, 嗜血杆菌属、梭杆菌属、卟啉单胞菌属、罗氏菌属和放线菌属等菌属较健康对照显著增加, 提示微生物失衡是促进 OLP 进展的关键因素, 其机制可能与局部免疫反应和炎症过程有关[9] [10]。

肠道菌群(GM)是一个复杂的动态系统[11]在人类健康和疾病中发挥着至关重要的作用。它是宿主免疫稳态的重要调节因子, 通过调节免疫应答、参与代谢、调节炎症介质等作用影响各种免疫和慢性炎症性疾病[12] [13], 包括肥胖、2 型糖尿病和非酒精性脂肪性肝病[14]。近年来, “肠-口轴”的概念为理解微生物群失调与 OLP 的关系提供了新的视角[15] [16]。口腔与肠道之间存在密切的微生物联系, 口腔微生物可向下迁移至肠道, 加重各种胃肠道疾病, 而肠道微生物可向上迁移至口腔, 影响口腔菌群结构[17]。肠道菌群失调并不局限于肠道疾病的发生, 它还可能通过微生物易位和炎症信号通路影响口腔微生物菌群失调相互作用[18]。虽然越来越多的证据表明肠道菌群在银屑病[19]、炎症性肠病[20]、关节炎[21]等慢性炎症性疾病中发挥重要作用, 但 GM 与 OLP 之间的具体关系尚未完全阐明。关于 GM 对 OLP 是否具有直接因果效应, 目前尚缺乏明确的证据。

为了探索 GM 在 OLP 中的因果作用, 同时尽量减少混杂因素和疾病状态对宿主的影响, 本研究创新性地利用 MR 方法研究 GM 与 OLP 的因果关系。MR 是一种基于遗传变异的因果推断方法, 将遗传变异作为工具变量来模拟随机对照试验的效果。由于遗传变异在出生时就已确定, 且不太可能受到环境因素或反向因果关系的影响, 因此 MR 可有效减少传统观察性研究中常见的混杂因素[22]。具体而言, 与 GM 组成相关的单核苷酸多态性(SNPs)被用作工具变量(IVs)来推断微生物群和 OLP 之间的因果关系。该方法评估了特定微生物群丰度的变化是否会增加或降低 OLP 的风险。MR 已被用于探索 GM 与各种疾病之间的潜在因果关系[23]。

2. 材料和方法

2.1. 数据来源

本研究的 GM 数据来自 MiBioGen 联盟, 该联盟对肠道菌群进行了开创性的全基因组关联研究(GWAS) [24]。本研究纳入了来自 11 个国家的 18,340 名参与者(24 个队列), 其中大多数为欧洲血统($n = 13,266$)。通过对汇总数据的仔细分析, 获得了微生物群的详细分类信息, 包括 211 个类群, 隶属于 131 属、35 科、20 目、16 纲、9 门。为保证分析的可靠性, 本研究排除了 12 个未知科和属, 纳入了 119 个属水平的类群作为随访研究的暴露。OLP 的 GWAS 数据来源于 FinnGen 数据库(<https://www.finnngen.fi/en>), 包括 795 例 OLP 患者和 499,553 例非 OLP 患者, 均来自欧洲[25]。

2.2. 工具变量的选择

工具变量(IVs)的选择必须满足三个关键假设。(1) 相关性假设: IVs 需要显示与暴露因素的强相关性;(2) 独立性假设: IVs 不应受到混杂因素的影响;(3) 排他性假设: IVs 不应该与结局相关。

为了确保有足够数量的 SNPs 用于分析, 我们将肠道微生物群 SNPs 的全基因组显著性阈值设定为 $p < 1 \times 10^{-5}$ 。我们进行了连锁不平衡(LD)聚集以确保 SNPs 是独立的($LD r^2 < 0.001$, LD 聚集距离= 10,000 kb)。去除 F 统计量 <10 的 SNP 以排除弱工具变量。此外, 回文 SNPs (带有 A/T 或 G/C 等等位基因的

SNPs)和结果中不存在的 SNPs 被排除。

2.2. 研究设计

在本研究中，GM 作为暴露因素，显著相关的 SNP 被选择为 IVs，OLP 作为结局变量。因果分析采用双样本 MR 方法进行，图 1 显示了当前研究设计的概述。

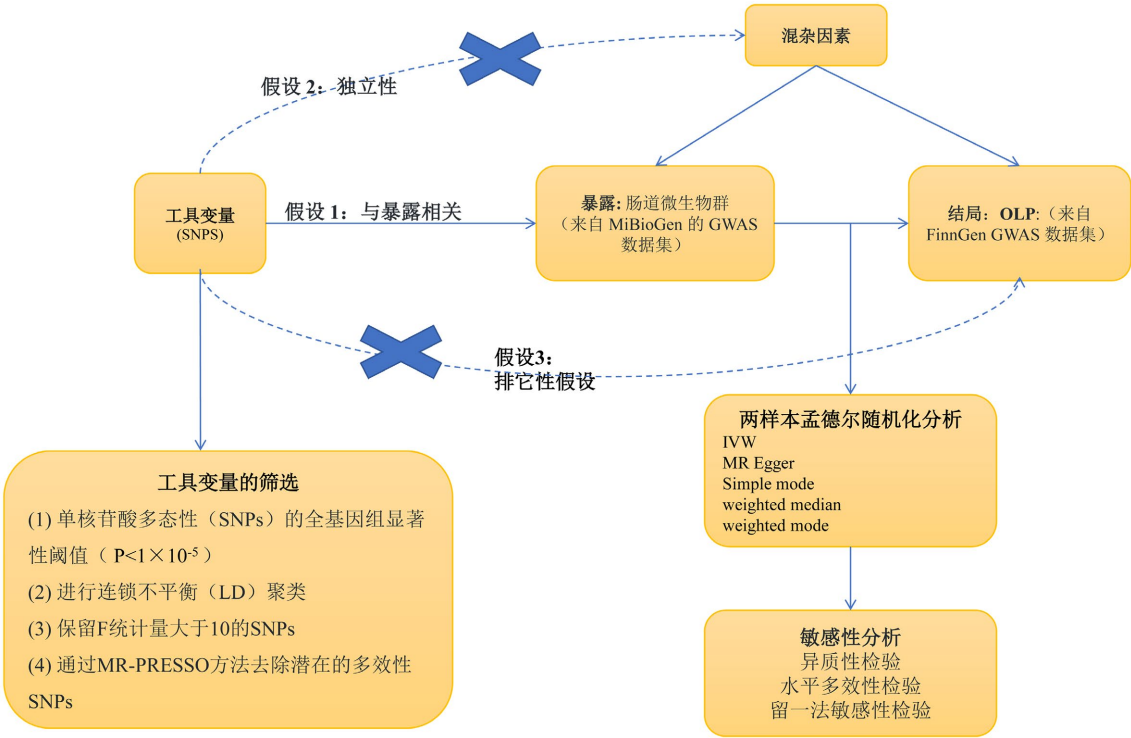
2.4. 统计方法

2.4.1. 孟德尔随机化分析

采用逆方差加权(IVW)方法评估 GM 与 OLP 的因果关系。这种包含随机效应的统计方法被认为是获得因果效应估计的最有效方法[26]。此外，采用 MR-Egger 回归、加权中位数、简单模态和加权模态 4 种补充方法进一步验证结果。当 IVW $p < 0.05$ 时，结果被认为是显著的；当 IVW 结果不存在异质性和多效性时，结果被认为是可靠的[27]。

2.4.2. 异质性和多效性检验

为保证结果的稳定性，进行了异质性和多效性检验。采用随机效应 IVW 的 Cochran’s Q 检验评估单个 SNP 效应的异质性， $p > 0.05$ 表示无异质性。MR-Egger 截距检验用于评估数据的多效性， $p < 0.05$ 表示其存在。MR-PRESSO 分析用于消除离群值并校正水平多效性。最后，使用留一法分析方法评估数据的稳健性，以确定每个 SNP 对结果的影响。所有统计分析均使用 R 软件(version 4.4.0)中的“Two Sample MR (version 0.6.1)”和“MR-presso (version 1.0)”软件包进行。



IVs: 工具变量, SNP: 单核苷酸多态性, OLP: 口腔扁平苔藓, MR: 孟德尔随机化, GWAS: 全基因组关联研究, IVW: 逆方差加权, LD: 连锁不平衡, MR-presso: MR 残差和多重性和离群值

Figure 1. Flow chart of study design
图 1. 研究设计流程图

2.5. 伦理声明和批准

本研究是对现有数据的二次分析，不需要额外的伦理批准。

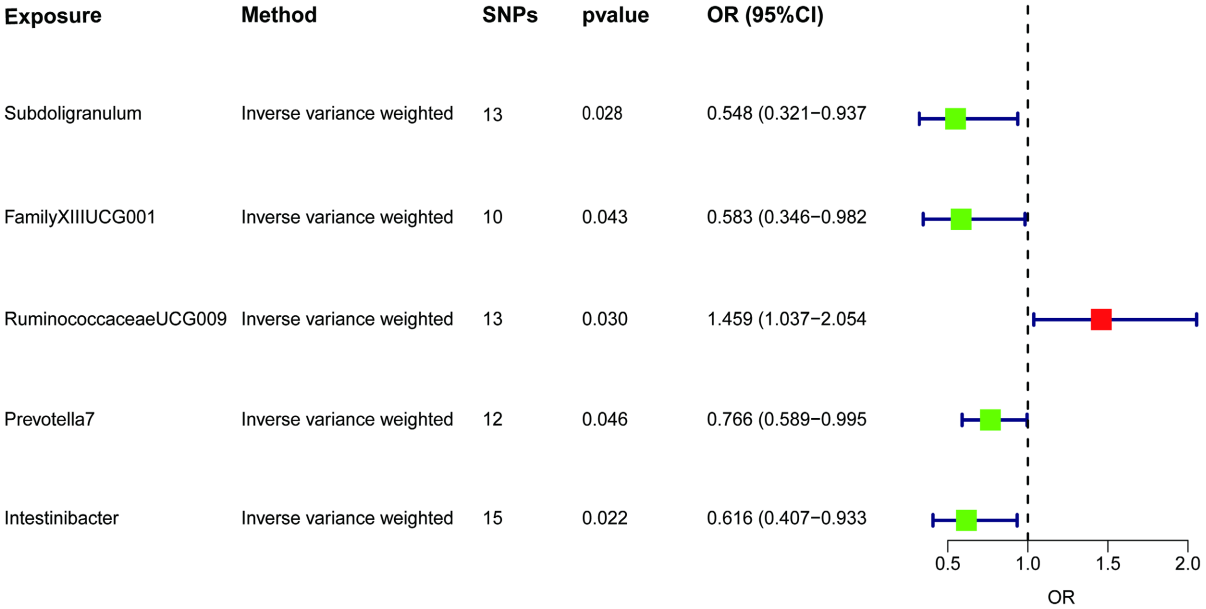
3. 结果

3.1. 工具变量(IVs)选择

根据 IVs 的筛选标准，共 1531 个 GM 相关 SNPs 被纳入研究。在本研究中，所有 IVs 的 F 统计值均大于 10，表明偏倚的可能性较低。

3.2. 肠道菌群对 OLP 的因果效应

通过孟德尔随机化分析，识别了与 OLP 风险指标相关的五个肠道菌群类群。根据 IVW 方法，四个菌群类群表现出对 OLP 的潜在保护作用，一个菌群类群与 OLP 风险增加相关(见图 2 和图 3)。具有保护作用的菌群类群包括 Subdoligranulum (比值比[OR]: 0.548, 95%置信区间[CI]: 0.321~0.937, $p=0.028$)、FamilyXIIIUCG001 (OR: 0.583, 95% CI: 0.346~0.982, $p=0.043$)、Prevotella 7 (OR: 0.766, 95% CI: 0.589~0.995, $p=0.046$)和 Intestinibacter (OR: 0.616, 95% CI: 0.407~0.933, $p=0.022$)。相比之下，Ruminococcaceae UCG009 (OR: 1.459, 95% CI: 1.037~2.054, $p=0.030$)与 OLP 风险增加相关。

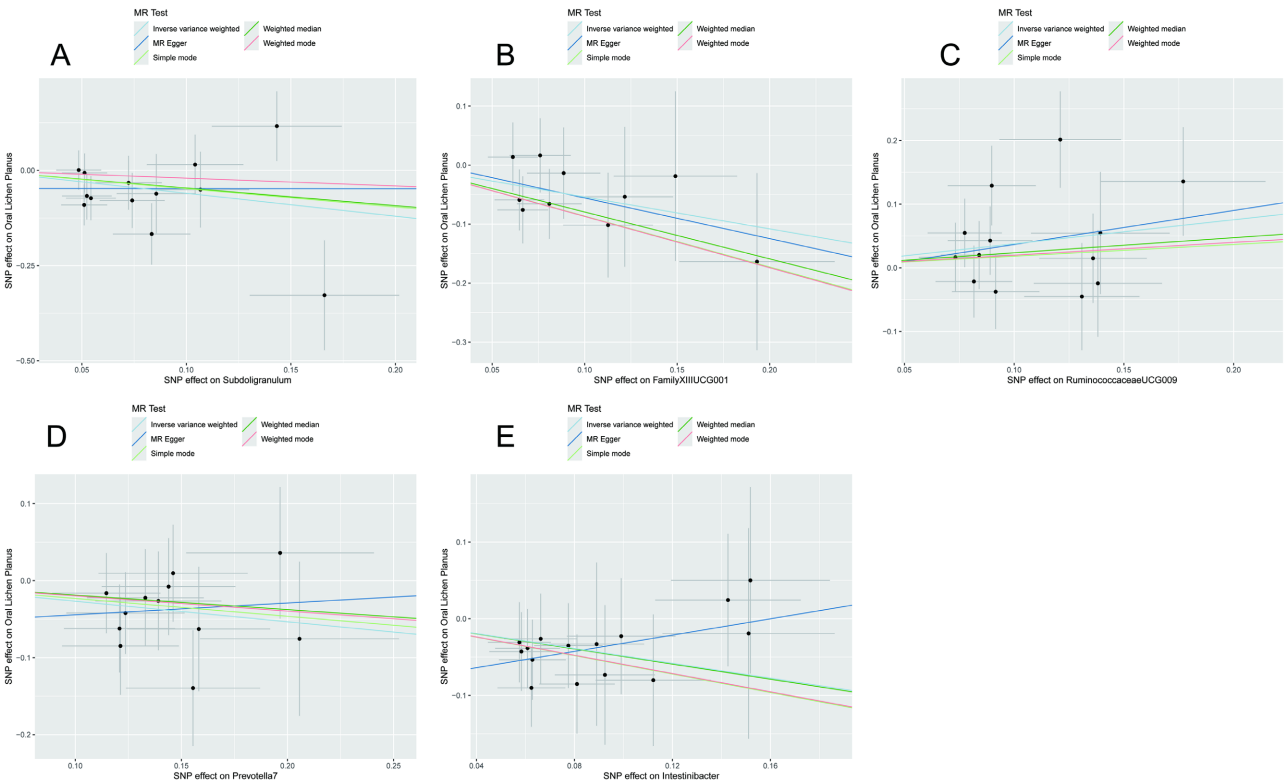


SNP: 单核苷酸多态性，OR: 比值比，CI: 可信区间。绿色为保护因素，红色为危险因素。

Figure 2. Forest plots of MR results for 5 gut microbiotas on OLP
图 2. 5 种肠道微生物对 OLP 影响的 MR 结果森林图

3.3. 敏感性分析结果

敏感性分析结果如表 1 所示。通过 Cochran’s Q 检验没有发现显著的异质性($p>0.05$, 表 1)。此外，MR-Egger 截距检验和 MR-PRESSO 分析表明没有显著的水平多效性($p>0.05$, 表 1)。留一法敏感性分析表明，去除单个 SNPs 后，结果没有显著变化，表明没有单个 IV 对总体效果产生过度影响(见图 4)。这些敏感性分析支持主要结果的稳健性。



Subdoligranulum (A), Family XIII UCG001 (B), Ruminococcaceae UCG009 (C), Prevotella 7 (D), and Intestinibacter (E).

Figure 3. Scatter plots of MR analysis on the causal relationship between 5 gut microbiotas and OLP

图 3. 5 种肠道菌群与 OLP 因果关系的 MR 散点图分析

Table 1. Sensitivity analysis of Mendelian randomization

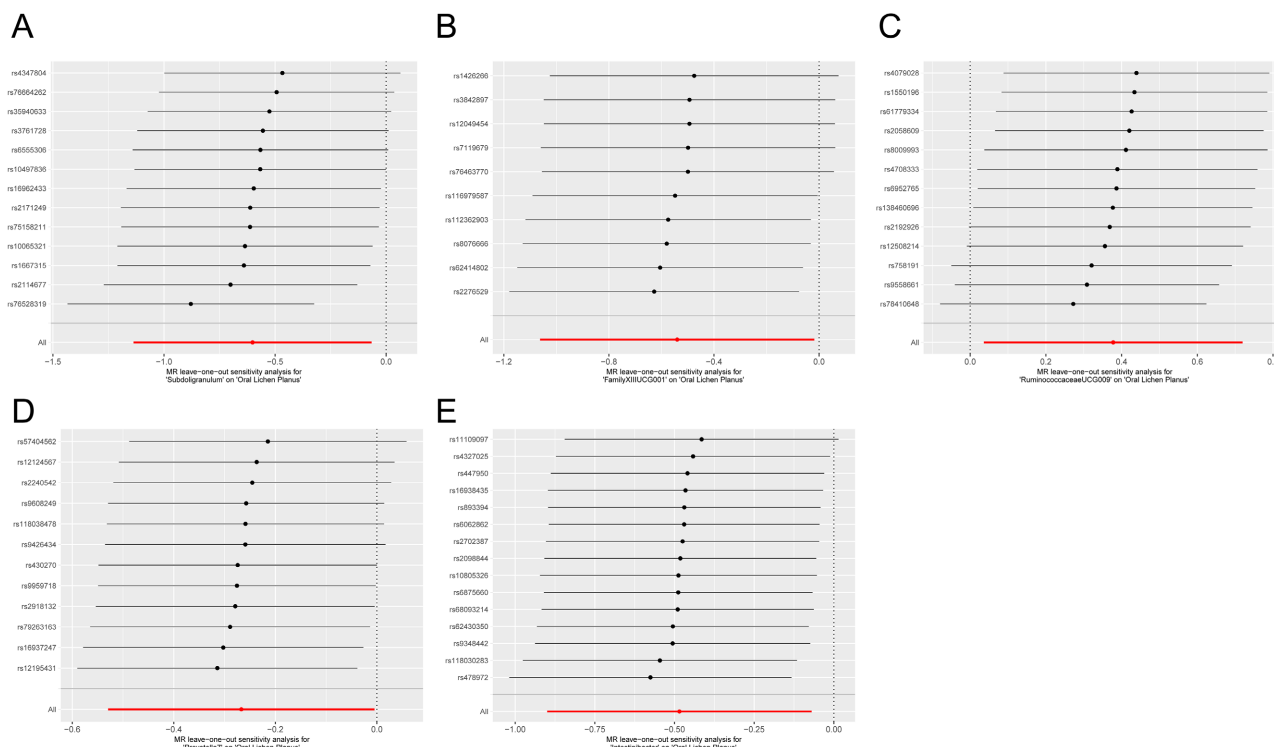
表 1. 孟德尔随机化的敏感性分析

暴露	异质性检验						多效性检验			MR-PRESSO <i>P</i>
	MR-Egger			Inverse variance weighted			MR-Egger			
	Q	Q_df	Q_pval	Q	Q_df	Q_pva	Egger intercept	se	pval	
Subdoligranulum	12.53445	11	0.324838	13.38421	12	0.341744	−0.04762	0.055138	0.406266	0.287
Family XIII UCG001	3.05855	8	0.93063	3.090721	9	0.960589	0.013159	0.073367	0.862114	0.964
Ruminococcaceae UCG009	12.19756	11	0.348978	12.25981	12	0.425046	−0.01673	0.070607	0.817069	0.432
Prevotella7	4.573534	10	0.917789	4.84767	11	0.938319	−0.05969	0.114	0.611976	0.948
Intestinibacter	2.488001	13	0.99924	4.882194	14	0.987386	−0.08511	0.055007	0.145778	0.987

Q: Heterogeneity static Q; df: Degree of freedom; se: Standard error

4. 讨论

OLP 的病因和发病机制尚未完全阐明,但普遍认为与免疫系统的异常调节和慢性炎症密切相关[28]。GM 作为宿主免疫系统的重要调节因子[29],可能通过其代谢产物及与宿主免疫系统的复杂相互作用在 OLP 的发生发展中发挥作用。



Subdoligranulum (A), Family XIII UCG001 (B), Ruminococcaceae UCG009 (C), Prevotella 7 (D), and Intestinibacter (E).

Figure 4. Leave-one-out plots of sensitivity analysis on 5 gut microbiotas and OLP

图 4. 5 种肠道菌群与 OLP 敏感性分析的留一法敏感性分析图

短链脂肪酸(SCFAs)是 GM 的重要代谢产物之一, 已被证明在调节免疫和抑制炎症中发挥重要作用[30] [31]。Subdoligranulum 是短链脂肪酸(SCFAs)的主要生产者之一, 尤其是丁酸[32]。丁酸可通过抑制 NF- κ B 信号通路显著降低促炎因子 IL-1 β 、IL-2、IL-6 的表达[33]-[35], 同时增加抗炎因子 IL-4、IL-10 的表达[33] [34] [36]-[38]。此外, 丁酸还能通过增强肠道屏障功能[39], 减少炎症因子的扩散。总体而言, SCFAs 在免疫调节中发挥着多重作用。它们不仅通过抑制 NF- κ B 信号通路减轻炎症反应, 还通过调节 T 细胞亚群如促进 Treg 细胞分化, 抑制 Th1 和 Th17 细胞的活性来维持免疫稳态。因此, Subdoligranulum 通过其丁酸代谢产物的抗炎作用可能与 OLP 发病风险的降低密切相关。

Family XII IUCG001 属于厚壁菌门, 现有研究提示其可能发挥改善脂代谢紊乱或协同维持肠道稳态的作用[40]。动物实验也表明, 这种微生物群可能具有抑制炎症的潜在作用[41] [42]。从免疫调节角度来看, 这种菌群可能通过影响肠道屏障功能, 减少有害物质的吸收, 进而减轻慢性炎症反应。然而, 其具体的免疫学机制仍需更多实验验证。

目前针对 Prevotella 7 的研究有限, 但现有的研究表明, Prevotella 在维持人体健康方面发挥着重要作用[43]。Prevotella 丰度的增加与胃肠道症状的改善密切相关[44] [45], Prevotella 通过抑制 TGF- β /Smad 信号通路, 减少 IL-6 释放, 在免疫调节中发挥重要作用。结合本研究的结果, Prevotella 7 与 OLP 风险降低的显著关联可能归因于其免疫调节和抗炎作用。作为健康肠道生态系统的一部分, 肠杆菌可能通过尚不完全清楚的抗炎途径发挥保护作用[46] [47]。需要进一步的研究来阐明肠杆菌在 OLP 中的具体作用机制。

Ruminococcaceae UCG009 的增加可能通过促进循环中葡萄糖和脂质的积累、增强促炎反应或破坏免疫稳态来潜在增加 OLP 的风险。研究表明, 某些 Ruminococcaceae 科菌株可以将植物多糖降解为葡萄糖, 刺激肝脏甘油三酯的产生, 并增加循环葡萄糖和血脂水平[48]。此外, 研究发现 Ruminococcaceae 家族与

血液 IgM 水平、结肠炎[49]呈正相关。这些证据表明, Ruminococcaceae 可能在各种炎症和免疫相关疾病中发挥重要作用。具体到 OLP, Ruminococcaceae UCG009 通过促进糖脂代谢紊乱, 可能通过增加 IL-6、TNF- α 等促炎因子的释放或通过 TLR4 信号通路激活 NF- κ B, 增强免疫反应, 从而加重 OLP 的炎症过程。

虽然随机对照试验(RCT)是确认病理机制与疾病之间因果关系的金标准, 但 RCT 的成本高、伦理约束和操作复杂性使其难以直接验证 GM 与 OLP 之间的因果关系。利用基因变异作为工具变量, MR 分析提供了一种可行的替代方法。在本研究中, 我们利用 MR 分析揭示了特定的 GM 与 OLP 风险之间的潜在因果关系, 有效降低了混杂因素的影响。然而, 本研究也存在一定的局限性。研究数据主要来源于欧洲人群的 GWAS 数据库, 这可能限制了结论对其他地区和民族的适用性。未来还需要更多的实验验证和更大规模的前瞻性研究来充分阐明肠道菌群在 OLP 发病机制中的作用。

尽管本研究采用了 MR 方法, 从遗传学角度探讨了肠道菌群与 OLP 之间的因果关系, 并初步揭示了肠道菌群可能通过某些机制影响 OLP 的发生发展, 但由于实验资源和技术条件的限制, 本研究暂时未能进一步通过动物模型或细胞实验验证这一假设的具体生物学机制。孟德尔随机化作为一种基于遗传变异的工具, 可以有效避免传统观察性研究中的混杂偏倚和逆因果关系的问题, 但其本身并不能直接揭示肠道菌群影响 OLP 的具体生物学途径或机制。因此, 未来的研究应进一步补充实验验证, 以从分子和细胞层面深入探讨肠道菌群在 OLP 发生中的具体作用。

5. 结论

在本研究中, 我们首次通过双样本 MR 系统地阐明了 GM 和 OLP 之间的潜在因果关系。研究结果表明, Subdoligranulum、Family XIII UCG001、Prevotella7 和 intestinalbacter 的丰度增加可能对 OLP 具有保护作用, 而 Ruminococcaceae UCG009 的丰度增加可能增加 OLP 的风险。这些发现为理解 GM 在 OLP 发病机制中的潜在作用提供了新的视角, 并提示特定微生物的调控可能是未来 OLP 防治的新策略。虽然通过严格的统计学方法验证了结果的稳健性, 但本研究仍有局限性, 结论可能不适用于其他地区人群, 需要进一步研究来充分揭示 GM 在 OLP 发病机制中的作用。

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