

·临床研究·

## 食物过敏伴便秘儿童肠道菌群变化与功能分析

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**摘要:**【目的】运用高通量测序, 了解食物过敏伴便秘儿童肠道菌群变化, 并进行功能分析, 为防治儿童食物过敏伴便秘提供依据。【方法】选取深圳市龙岗区妇幼保健院患有食物过敏伴便秘儿童33例作为疾病组(CPFA), 选取59例该院儿童保健科的同龄健康儿童作为健康组(HC)。收集受试者的粪便标本, 对标本进行16SrRNA基因高通量测序并分析。【结果】①HC组物种丰度高于CPFA组, 两组肠道微生物群落多样性有差异; ②门水平, 与HC组相比, CPFA组拟杆菌门、脱硫杆菌门相对丰度低, 厚壁菌门、放线杆菌门、变形杆菌门相对丰度高( $P<0.05$ ); ③属水平, 与HC组相比, CPFA组拟杆菌属、副拟杆菌属相对丰度低, 双歧杆菌属、埃希氏-志贺氏菌属、韦荣氏球菌属相对丰度高( $P<0.05$ ); ④功能分析显示, 两组间存在显著差异的功能基因, 与HC组相比, CPFA组在缬氨酸、亮氨酸和异亮氨酸的生物合成、半胱氨酸和蛋氨酸代谢、脂肪酸代谢、金黄色葡萄球菌感染等的功能基因丰度显著增加( $P<0.05$ )。与胆汁酸生物合成、视黄醇代谢等有关的功能途径的功能基因丰度显著降低( $P<0.05$ )。【结论】食物过敏伴便秘儿童肠道菌群及功能与健康儿童存在差异, 这可能有助于探秘食物过敏伴便秘的发病机制, 并为新的治疗干预提供理论基础。

**关键词:** 食物过敏; 便秘; 肠道菌群; 菌群功能; 高通量测序

中图分类号: R725.7

文献标志码: A

文章编号: 1672-3554(2025)02-0345-09

DOI: 10.13471/j.cnki.j.sun.yat-sen.univ(med.sci).2025.0219

## Changes and Functions Analysis of Intestinal Flora in Children with Food Allergy and Constipation

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**Abstract:**【Objective】To investigate the changes of intestinal flora in children with food allergy and constipation by high-throughput sequencing, and to analyze the function of intestinal flora, to provide a basis for the prevention and treatment of food allergy and constipation in children.【Methods】Totally 33 children with food allergy and constipation in Longgang District of Shenzhen were selected as the disease group (CPFA group), another 59 healthy children of the same age were recruited as the HC group. Stool samples were collected and subjected to high-throughput sequencing of 16SrRNA genes, followed by bioinformatics analysis.【Results】① The species abundance of HC group was higher than that of CPFA group, and the diversity of intestinal microbial community was different between the two groups; ② At the phylum level, the relative abundance of *Bacteroidota*, *Desulfobacterota* in CPFA group was lower than that in HC group, and the relative abundance of *Firmicutes*, *Actinobacteria* and *Proteobacteria* in CPFA group was higher than that in HC

收稿日期: 2024-10-13

录用日期: 2025-02-19

基金项目: 深圳市龙岗区科技创新局基金(LGWJ2023-038); 深圳市龙岗区妇幼保健院院级课题科研启动基金(Y2024011)

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Group ( $P < 0.05$ ); ③ At the genus level, the relative abundance of *Bacteroids*, *Parabacteroides* in the CPFA group was lower than that in the HC group, and the relative abundance of *Bifidobacterium*, *Escherichia-Shigella* and *Veillonella* in the CPFA group was higher than that in the HC group; ④ Functional analysis showed that there were significant differences in functional genes between the two groups. Compared with those in the HC group, the abundance of functional genes in valine, leucine and isoleucine biosynthesis, cysteine and methionine metabolism, fatty acid metabolism and *Staphylococcus aureus* infection were significantly increased in the CPFA group ( $P < 0.05$ ). The abundance of functional pathways related to bile acid biosynthesis and retinol metabolism was significantly decreased ( $P < 0.05$ ). 【Conclusion】 There are differences in intestinal flora and function between children with CPFA and HC, which may help to explore the pathogenesis of food allergy and constipation, and provide a theoretical basis for new therapeutic interventions.

**Key words:** food allergy; constipation; intestinal flora; microbiota function; high-throughput sequencing

[J SUN Yat-sen Univ (Med Sci), 2025, 46(2): 345-353]

食物过敏是指暴露于某种特定食物时出现的由特异免疫反应引起的不良健康影响,也可定义为由食物引起的对人体有害的免疫反应<sup>[1]</sup>。目前,食物过敏已成为一个全球性的公共问题。在美国,约有8%的儿童受到食物过敏的影响<sup>[2]</sup>。中国温州地区3~6岁儿童食物过敏发生率为12.86%<sup>[3]</sup>。在食物过敏的儿童中便秘是比较常见的伴随症状。食物过敏伴便秘患儿在婴儿时期可表现为腹泻、干呕、呃逆等,后续可发展为便秘、皮炎或呼吸道疾病<sup>[4]</sup>。一些患食物过敏的儿童从婴儿起的腹泻转为便秘是食物过敏患儿最常见的延迟性临床表现。目前认为食物过敏可能是引起儿童功能性便秘的常见原因<sup>[5]</sup>,但相关机制尚未完全清晰。近年来,食物过敏儿童的肠道菌群变化已成为研究的热点。多项研究表明食物过敏儿童与健康儿童的肠道菌群存在一定差异<sup>[6-7]</sup>。便秘与肠道菌群的关系也有报道,李辉等<sup>[8]</sup>研究认为功能性便秘婴幼儿存在肠道菌群结构和多样性的改变。Yarullina等<sup>[9]</sup>的研究结果表明便秘患者的肠道微生物群由典型的肠道细菌组成,并且存在显著的个体差异。食物过敏易发生便秘是否与肠道菌群改变相关,是否通过肠道微生物代谢活动相互促进,目前这方面研究少见报道。本研究拟探讨食物过敏伴便秘患儿肠道菌群的变化及功能预测,为食物过敏伴便秘相关机制研究提供理论依据。

## 1 材料与方 法

### 1.1 对 象

选取深圳市龙岗区妇幼保健院患有食物过敏

伴便秘儿童33例,作为疾病组(food allergy and constipation, CPFA组);选取59例该院儿保科体检的同龄健康儿童作为健康组(healthy children, HC组)。入组标准:①年龄0.6~3岁;②符合食物过敏诊断标准<sup>[1]</sup>及儿童功能性便秘诊断标准<sup>[10]</sup>;排除标准:①慢性消化系统疾病,如炎症性肠病、溃疡性结肠炎等;②入选前有药物干预,包括肠动力药物、抗胆碱能药物、利福平等,以及4周内使用抗生素和益生菌者;③严重精神障碍,如抑郁症、心理障碍等。本研究经深圳市龙岗区妇幼保健院医院伦理委员会审核批准(编号:LGFKYXMLL-2024-66)。入组患儿及健康儿童均获得监护人的书面知情同意。

### 1.2 方 法

1.2.1 儿童食物过敏诊断标准 ①病史:进食出现以下1项或多项临床表现,包括皮肤症状如风团、弥漫性瘙痒、面部潮红、血管性水肿,胃肠道症状如呕吐、腹泻、便血、便秘,呼吸道症状如咳嗽、喘鸣、呼吸困难及发育不良等;②食物回避后症状减轻或消失,再引入后症状加重或再次出现;③以下实验室检查有1项或多项阳性,血清过敏原特异性IgE ( $>0.35$  kU/L),口服食物激发试验,皮肤点刺试验<sup>[1]</sup>。

1.2.2 罗马IV儿童功能性便秘诊断标准 <4岁儿童,符合以下至少2项条件,且症状持续至少1个月:①每周排便次数不大于2次;②有大量粪便潴留病史;③有排便疼痛和排便费劲病史;④排粗大粪便史;⑤直肠内存在大量粪块;⑥能控制排便后每周出现至少1次大便失禁;⑦粗大粪块曾堵塞马桶<sup>[10]</sup>。

1.2.3 样本采集和测序 收集两组儿童的粪便标本,取中段粪便的中心部位5g左右,采集后立即冷

冻,保存于-80℃冰箱,干冰运送到华大精准营养科技有限公司进行高通量测序。采用Mobio公司的PowerEarth DNA对样本提取总DNA,随后对DNA样本进行16SrRNA基因V4区域PCR扩增。采用Illumina公司的NovaSeq 6000平台,SP-Xp(PE250)的双端测序策略进行测序,测序后进行生物信息学分析。

### 1.3 测序结果分析

首先对原始数据使用FLASH2软件将双末端测序得到的成对序列进行拼接,拼接的序列使用usearch去除总碱基错误率大于2的序列以及长度小于100 bp的序列,得到质量和可信度较高的优化序列,将其分为不同的操作分类单元(OTU),将每条OTU代表序列与Silva数据库进行比对从而完成OTU的分类学注释。根据OTU表,对两组儿童样本Alpha多样性进行分析:计算菌群多样性的指数Simpson。对样本在属水平上的组成和相对丰度,进行主坐标分析(PCoA)。对两组儿童整体菌群分布绘制柱状图,在门和属水平分布情况进行差异分

析。对两组间肠道菌群进行功能预测分析。

### 1.4 统计学方法

本研究使用R软件进行,两组间多样性指数差异分析及整体菌群在门和属水平分布差异分析及菌群功能预测分析均采用Wilcoxon分析,以 $P<0.05$ 作为差异显著性筛选阈值,对于组间相对丰度显著差异的功能绘制箱体图;两组间菌群差异性比较采用在基线水平对两组样本进行基于unifrac距离算法的主坐标分析(principalco-ordinates analysis, PCoA);对功能组成绘制柱状图。一般资料采用SPSS 29.0统计分析, $P<0.05$ 为差异有统计学意义。

## 2 结果

### 2.1 一般临床资料

两组儿童在年龄、性别、体质量之间比较差异无统计学意义( $P>0.05$ )。两组儿童基线资料具有可比性(表1)。

表1 两组儿童一般临床资料比较

Table 1 The general clinical data of the two groups

( $\bar{x} \pm s$ )

Groups	<i>n</i>	Age/years	Gender(male/female)	Weight/kg
CPFA	33	1.69±0.65	20/13	10.76±1.61
HC	59	1.86±0.66	33/26	11.34±1.70
<i>t</i> / $\chi^2$		0.123	0.189*	0.054
<i>P</i>		0.726	0.663	0.817

\*  $\chi^2$  value.

### 2.2 CPFA组肠道微生物物种多样性降低

比较两组儿童肠道菌群的多样性和组成,结果显示:①两组样本微生物群Simpson指数存在明显的差异(注Simpson指数越高,菌群多样性越低,反之,多样性越高),CPFA组Simpson指数高于HC组,说明CPFA组群落多样性低于HC组,且有统计学差异( $Z=4.355, P<0.0001$ ;图1)。②主成分分析显示,HC组微生物群落的置信椭圆与CPFA组的置信椭圆有明显偏差,说明两组肠道微生物物种多样性也存在明显差异(图2)。

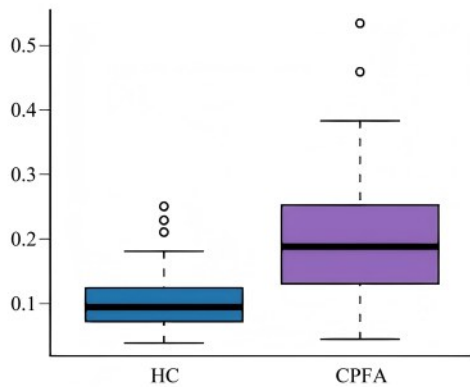
### 2.3 门水平优势菌门及差异性分析

门水平菌群检测显示:门水平优势菌门分别为拟杆菌门(*Bacteroidota*)、厚壁菌门(*Firmicutes*)、变

形杆菌门(*Proteobacteria*)、放线杆菌门(*Actinobacteriota*)、脱硫杆菌门等(*Desulfobacterota*)等(图3)。与HC组相比,CPFA组拟杆菌门( $Z=-7.892, P<0.0001$ )、脱硫杆菌门( $Z=-3.533, P<0.001$ )相对丰度低,而厚壁菌门( $Z=2.857, P<0.01$ )、放线杆菌门( $Z=3.399, P<0.001$ )、变形杆菌门( $Z=1.966, P<0.05$ )相对丰度高(图4)。

### 2.4 属水平优势菌属及差异性分析

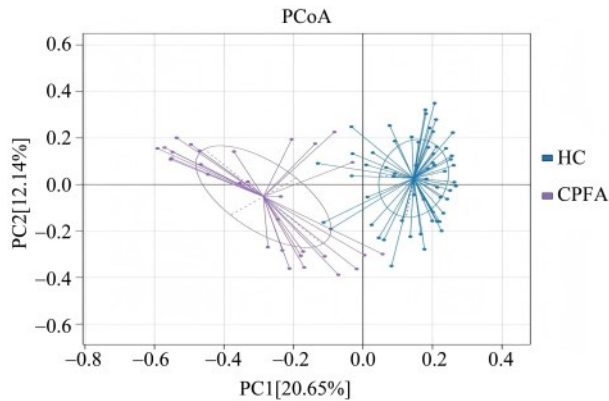
结果提示属水平优势菌属有:拟杆菌属(*Bacteroides*)、双歧杆菌属(*Bifidobacterium*)、埃希氏-志贺氏菌属(*Escherichia-Shigella*)、韦荣氏球菌属(*Veillonella*)、副拟杆菌属(*Parabacteroides*)等(图5)。与HC组相比,CPFA组拟杆菌属



The community diversity of the CPFA group is significantly lower than that of the HC group. CPFA group  $n=33$ , HC group  $n=59$ .  $P < 0.0001$ .

图1 两组肠道微生物物种多样性Simpson指数箱体图

Fig. 1 Simpson's index box diagram of species diversity in two groups of intestinal microecology



There are significant differences in the diversity of intestinal microbiota species between the two groups. CPFA group  $n=33$ , HC group  $n=59$ .

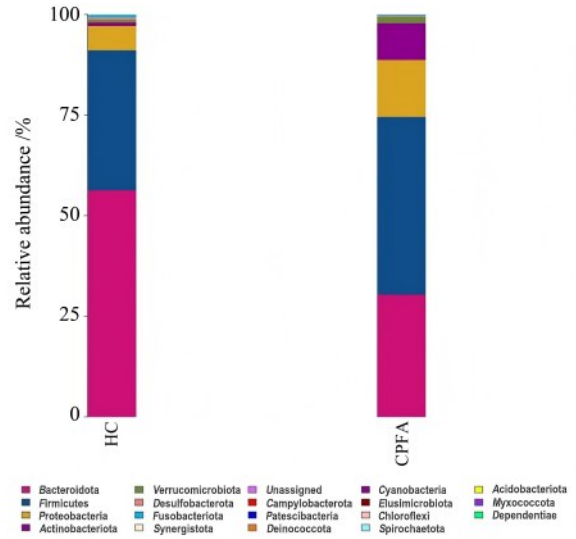
图2 两组肠道微生物物种组成差异性比较图

Fig. 2 Comparison of species composition of intestinal microecology between the two groups

( $Z=3.700$ ,  $P < 0.001$ )、副拟杆菌属 ( $Z=3.028$ ,  $P < 0.01$ ) 相对丰度低, 双歧杆菌属 ( $Z=3.785$ ,  $P < 0.001$ )、埃希氏-志贺氏菌属 ( $Z=3.370$ ,  $P < 0.001$ )、韦荣氏球菌属 ( $Z=7.811$ ,  $P < 0.0001$ ) 相对丰度高, 两组间差异均有统计学意义(图6)。

2.5 两组间肠道菌群功能预测分析

肠道菌群组成的差异会导致肠道菌群功能特征的差异。①图7列出了两组间存在显著差异的功能特征以及在各组的比例, 置信区间以及  $P$  值(图7)。②与HC组相比, CPFA组在缬氨酸、亮氨酸和异亮氨酸的生物合成 (valine, leucine and isoleucine biosynthesis) ( $Z=3.358$ ,  $P < 0.001$ )、半胱氨



The dominant bacterial phylum in the two groups. CPFA group  $n=33$ , HC group  $n=59$ .

图3 两组间门水平菌落柱状图

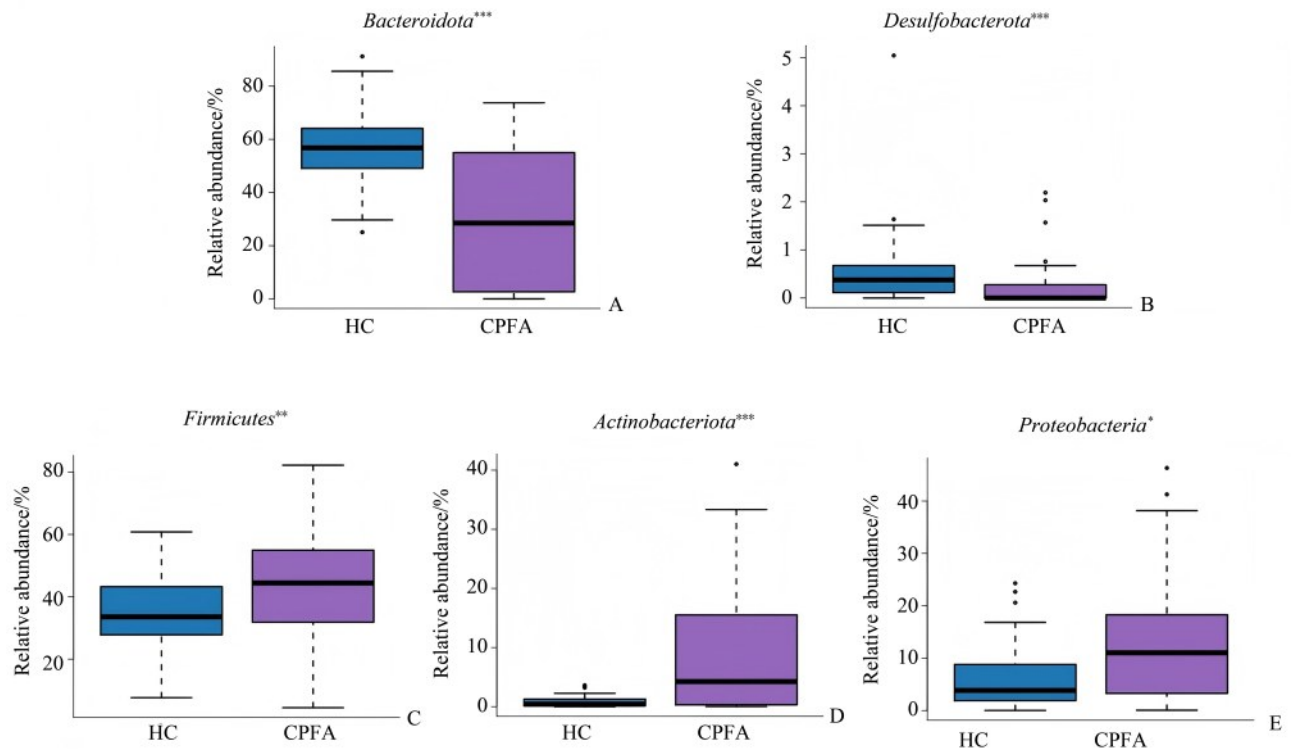
Fig. 3 Horizontal colony histogram in the phylum level between two groups

酸和蛋氨酸代谢 (cysteine and methionine metabolism) ( $Z=3.492$ ,  $P < 0.001$ )、脂肪酸代谢 (fatty acid metabolism) ( $Z=3.761$ ,  $P < 0.001$ )、金黄色葡萄球菌感染 (staphylococcus aureus infection) ( $Z=7.192$ ,  $P < 0.0001$ ) 等的功能丰度显著增加(图8)。与胆汁酸生物合成 (primary bile acid biosynthesis) ( $Z=-3.448$ ,  $P < 0.001$ )、视黄醇代谢 (retinol metabolism) ( $Z=-5.764$ ,  $P < 0.0001$ ) 等有关的功能途径的丰度显著降低(图8)。

3 讨论

3.1 食物过敏伴便秘儿童肠道菌群多样性降低, 与正常儿童菌群存在差异

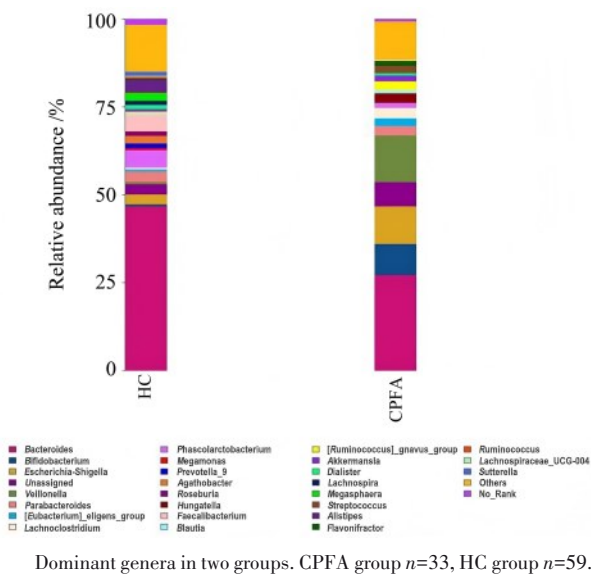
肠道菌群与很多疾病的发生和发展密切相关, 比如食物过敏及便秘儿童均存在肠道菌群失调<sup>[11-12]</sup>。肠道菌群能帮助保持黏膜屏障的完整性, 它通过防止细菌入侵维持肠上皮完整性, 而且, 微生物群与黏膜免疫系统之间的相互作用对维持适当的免疫功能发挥重要作用。有研究发现抗生素引发的小鼠肠道菌群丰度和多样性降低会引发小鼠肠道发生肠绒毛破裂, 紧密连接蛋白减少, 导致其食物过敏的加重<sup>[11]</sup>。本研究提示食物过敏伴便秘组儿童肠道菌群多样性明显低于健康组儿童, 且两组肠道微生物种群落有差异性, 这表明 CPFA



The relative abundances of *Bacteroidota* and *Desulfobacterota* were lower, and the relative abundances of *Firmicutes*, *Actinobacteria*, *Proteobacteria* were higher in the CPFA group. CPFA group  $n=33$ , HC group  $n=59$ . \* $P<0.05$ , \*\* $P<0.01$ , \*\*\* $P<0.001$ , \*\*\*\* $P<0.0001$ .

图4 两组间门水平优势菌差异性比较

Fig. 4 Comparison of the difference of the dominant bacteria in the phylum level between the two groups



Dominant genera in two groups. CPFA group  $n=33$ , HC group  $n=59$ .

图5 两组间属水平菌落柱状图

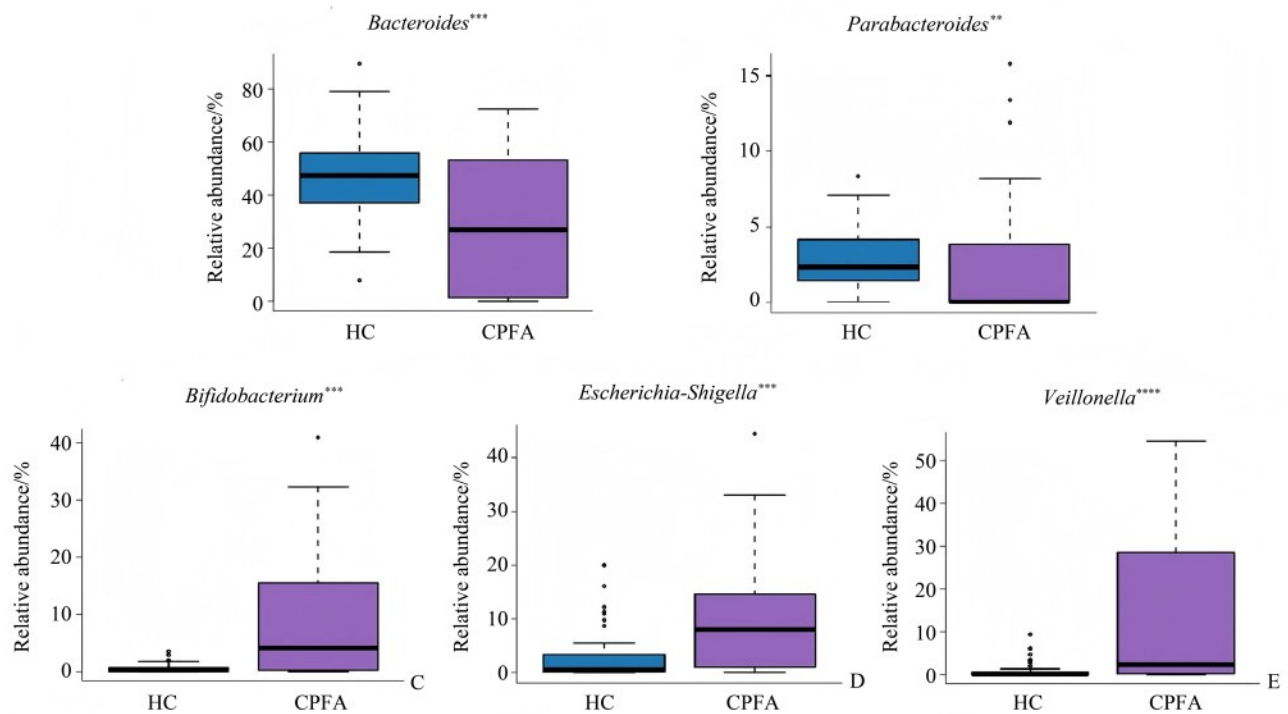
Fig. 5 Horizontal colony histogram in the genus level between two groups

组肠道微生物组成结构上与HC组有显著不同,过敏伴便秘与肠道菌群之间存在着相关性。这类患儿肠道微生态多样性降低可能通过影响肠道黏膜

的完整性从而触发过敏及便秘。

### 3.2 食物过敏伴便秘儿童肠道菌群改变诱发或加重肠道炎症

发现两组菌群组成差异后,本研究进一步探讨两组在门、属水平上的菌群差异。CPFA组儿童中属于拟杆菌门的拟杆菌属、副拟杆菌属相对丰度低(图6A,B),分别属于厚壁菌门、放线杆菌门、变形杆菌门的韦荣氏球菌属、双歧杆菌属、埃希氏-志贺氏菌属相对丰度高(图6C,D,E)。拟杆菌属维持人体肠道健康中起着关键作用,参与了碳水化合物的发酵、含氮物质的利用以及胆汁酸和其他类固醇的生物转化,它们能够产生短链脂肪酸和次级胆汁酸,对宿主有益<sup>[13]</sup>。副拟杆菌属能够分泌乙酸盐、丙酸盐等短链脂肪酸,也可以调节宿主黏膜免疫系统、减轻炎症,并参与碳水化合物利用<sup>[14-15]</sup>。de Meij等<sup>[16]</sup>对比了76例功能性便秘儿童和61例健康儿童(年龄中位数分别为8.0岁和8.6岁)的粪便菌群,发现功能性便秘患儿的粪便样本中脆弱拟杆菌、卵形拟杆菌、长双歧杆菌和副拟杆菌的菌种增加。Huang等<sup>[17]</sup>也报道了脑性瘫痪伴便秘患儿肠



The relative abundances of *Bacteroides* and *Parabacteroides* were lower in the CPFA group while the relative abundances of *Bifidobacterium*, *Escherichia-Shigella* and *Veillonella* were higher. CPFA group  $n=33$ , HC group  $n=59$ . \*\* $P<0.01$ , \*\*\* $P<0.001$ , \*\*\*\* $P<0.0001$ .

图6 两组间属水平优势菌差异性比较

Fig. 6 Comparison of the difference of the dominant bacteria in the genus level between the two groups

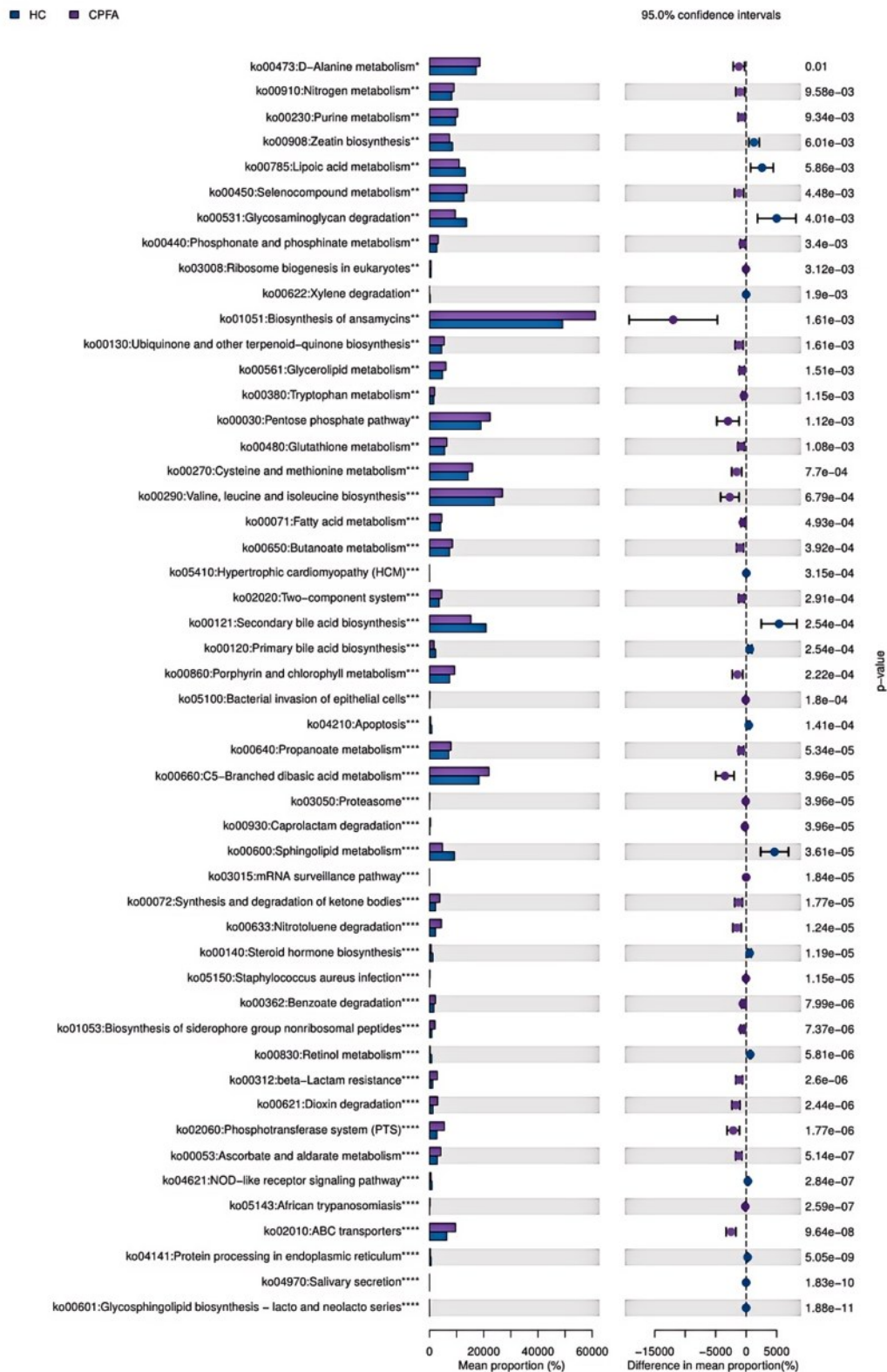
道中双歧杆菌丰度的显著增加,以及便秘改善后双歧杆菌丰度的下降。因此,我们认为双歧杆菌属丰度升高与便秘儿童相关,但双歧杆菌属亚种较多,本研究未进行宏基因组测序,无法明确与便秘相关的亚种。埃希氏-志贺氏菌属是一种条件致病菌,其特征是侵袭和炎症性破坏人类结肠上皮,可导致肠道黏膜出现炎症<sup>[18-19]</sup>。韦荣氏球菌属作为肠道微生物群中的主要成员之一,产生内毒素和其他代谢产物影响肠道屏障功能,增加肠道通透性<sup>[20]</sup>。从上述文献可以发现,CPFA组儿童肠道菌群的失调导致碳水化合物及胆汁酸的代谢功能下降,肠道黏膜出现慢性炎症,促进便秘发生发展。

### 3.3 食物过敏伴便秘儿童肠道菌群功能分析

本研究中发现两组儿童在50种功能代谢途径存在差异(图7)。图8列举了其中6个在目前研究中考虑与过敏、便秘相关的可能功能途径<sup>[21]</sup>。CPFA组儿童肠道菌群中与胆汁酸生物合成、视黄醇代谢等有关的功能途径的丰度显著降低(图8E,F)。脱硫杆菌门被认为参与了肠肝循环,是调节胆汁酸代谢中的重要一环。在对原发性胆汁性胆管炎对熊去氧胆酸治疗反应不足相关的细菌研究中发现,

对熊去氧胆酸治疗者中有反应者,肝功能较差组的粪便二级和三级胆汁酸含量较低,具有胆汁酸解离能力的门类如脱硫杆菌门的水平也较低<sup>[22]</sup>。本研究发现,CPFA组脱硫杆菌门相对丰度低,这提示可能影响肠道中胆汁酸的含量,从而促进便秘的产生。

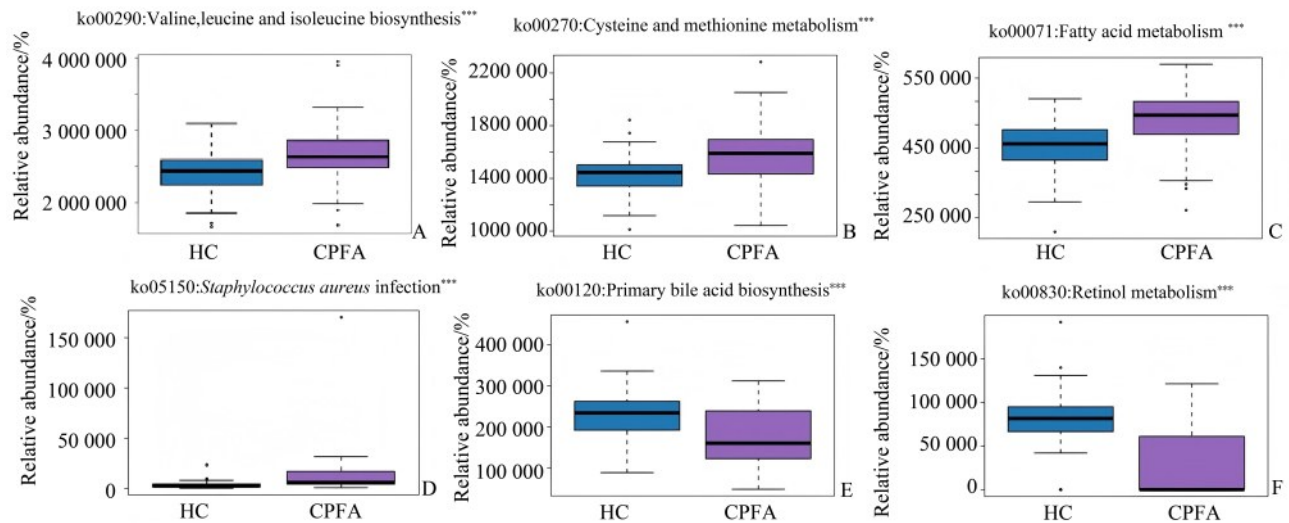
CPFA组儿童中参与碳水化合物代谢的菌属如拟杆菌属、副拟杆菌属丰度明显降低,而肠道菌群功能分析显示他们的氨基酸和脂肪代谢上调(图8A,B,C),提示CPFA组儿童可以通过适当减少摄入动物性食物,多食用蔬菜类食物来改善过敏伴便秘情况。CPFA组儿童肠道菌群功能中视黄醇代谢下调(图8F),视黄醇是维生素A家族的一员,肠道视黄醇浓度的平衡对于维持肠道内的免疫稳定状态起着非常重要作用<sup>[23]</sup>,提示可以通过补充维生素A来维持食物过敏伴便秘儿童肠道免疫稳态。金黄色葡萄球菌与食物过敏相关,是食物过敏的危险因素<sup>[24]</sup>,在本研究中亦发现CPFA组儿童肠道菌群功能中金黄色葡萄球菌感染等的功能上调(图8D),与韦荣氏球菌属、埃希氏-志贺氏菌属等丰度升高可能有关。肠道菌群功能分析是一个复杂的



The statistically significant functional features of two groups of gut microbiota, with 95% confidence intervals and *P* values on the right. The pathways marked by red boxes are currently considered potential routes related to allergies and constipation. CPFA group *n*=33, HC group *n*=59. \**P*<0.05, \*\**P*<0.01, \*\*\**P*<0.001, \*\*\*\**P*<0.000 1.

图7 两组肠道菌群功能特征差异柱状图

Fig. 7 Histogram of functional characteristics of intestinal flora between the two groups



There lists six functionally distinct pathway variants. The abundance of functional genes in valine, leucine and isoleucine biosynthesis, cysteine and methionine metabolism, fatty acid metabolism and *Staphylococcus aureus* infection was significantly increased in the CPFA group. The abundance of functional pathways related to bile acid biosynthesis and retinol metabolism was significantly decreased. CPFA group  $n=33$ , HC group  $n=59$ . \*\*\* $P<0.001$ , \*\*\*\* $P<0.0001$ .

图8 肠道菌群功能差异箱体图

Fig. 8 Box plot of functional differences in gut microbiota

过程,它通过对微生物群落的深入分析,帮助我们加深对肠道菌群在食物过敏伴便秘儿童中作用的理解。

综上所述,本研究初步展示了食物过敏伴便秘儿童肠道微生物群特点和功能代谢方面可能存在的差异,提示食物过敏伴便秘儿童的治疗有可能可以从着力于改善肠道微生态,促进肠道菌群均衡方面进行;可能有助于开发食物过敏伴便秘儿童的新

型治疗方法。

本研究也存在不足,如样本量偏少;选取的是一个时间点的横断面研究,没有进一步观测食物过敏伴便秘儿童在过敏食物消除后肠道菌群的动态变化等。今后可进行大样本及多中心研究,延长随访时间,动态监测患儿肠道菌群的变化。通过测序和代谢组学等方法更深入地探讨肠道菌群参与食物过敏伴便秘儿童具体作用机制。

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(编辑 孙慧兰)