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Relationship between intestinal flora, inflammation, BDNF gene polymorphism and generalized anxiety disorder

A clinical investigation

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Abstract

Introduction: Understanding factors related to generalized anxiety disorder pathogenesis is critical for elucidating the mechanism and preventing its establishment. Intestinal flora and hereditary factors such as brain-derived neurotrophic factor (BDNF) gene polymorphism may have a role in the development of generalized anxiety disorder. This work explored the relationship between intestinal flora, inflammatory changes and BDNF gene polymorphisms and the occurrence of generalized anxiety disorder.

Methods: Forty-eight patients with generalized anxiety disorder and 57 healthy people were included in the study. As the disease group and control group, the polymorphisms of rs10767664 and rs7124442 of the BDNF gene, differences in the distribution of intestinal flora, and changes in inflammatory and immune indicators were analyzed.

Results: The distribution of BDNF gene alleles, genotypes and haplotypes in the disease group were different from those in the control group. The levels of TNF-α (P = .000), interleukin-4 (P = .000), interleukin-10 (P = .043) and IgG (P = .008) in patients with generalized anxiety disorder in the disease group were different from those in the control group. The distribution of gut microbes in patients with generalized anxiety disorder in the disease group was different from that in the control group.

Conclusion: The onset of generalized anxiety disorder is related to BDNF gene polymorphism, and is accompanied by changes in intestinal flora and inflammatory immune status in the body.

Abbreviations: BDNF = brain-derived neurotrophic factor, DNA = deoxyribonucleic acid, GAD = generalized anxiety disorder, IL = interleukin, PCR = polymerase chain reaction.

Keywords: BDNF, gene polymorphism, generalized anxiety disorder, intestinal flora

1. Introduction

Generalized anxiety disorder (GAD) belongs to anxiety neurosis, patients of which display varying degrees of worry and anxiety toward various things. GAD is characterized by excessive agitation of autonomic nerve and excessive response to external things, accompanied with muscular tension.[1–3] GAD has a prevalence of over 5%, affecting women more than men, and is often diagnosed in children and adolescents.[4] GAD patients often develop other anxiety disorders such as phobia and depressive disorder, worsening their condition.[5] Though the etiology is not fully elucidated, GAD seems to be associated with altered secretion of 5-HT and norepinephrine, and the reduction of cerebral blood flow caused by cerebrovascular change and the alteration of blood viscosity. In addition, cerebral metabolism and inflammation level are also involved.[6,7] However, the development of GAD is more concerned with genetics, like gene polymorphism, with distinct features of

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The experiment was approved by the Ethics Committee of the Shandong Mental Health Center, and all patients participating in this study provided written informed consent in accordance with the "Helsinki Declaration".

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family aggregation.[8,9] Discovering factors that are related to GAD pathogenesis is meaningful to elucidate the mechanism and prevent the oncome of this disease.

Intestinal flora affects many diseases through acting locally or systemically, and their alteration is one of the main causes of diseases.[10,11] The potential pathological change such as inflammation and stress status of many diseases might be attributed to microbiota change.[12,13] Brain-derived neurotrophic factor (BDNF) is a neurotrophin that can improve neural function.[14] Previous studies proved that hereditary variabilities such as BDNF gene polymorphism is related to the development of mental diseases.[15,16]

Therefore, intestinal flora, inflammation, immunological reaction and rs10767664 and rs7124442 polymorphisms in BDNF gene of 48 GAD patients and 57 healthy people were analyzed in this study, aiming to determine the susceptibility factor of the disease and provide important evidence for elucidating the pathogenesis of GAD.

2. Methods

2.1. Patients and ethical statement

Forty-eight GAD patients were treated in our hospital from January 2019 to January 2020, and 57 healthy people were included in the study and were set as disease and control groups, respectively. GAD patients in the disease group met the diagnostic criteria of Chinese Classification and Diagnostic Criteria for Mental Disorders, third edition. The disease group included 20 male and 28 female GAD patients, and the median age was 41.24 ± 3.82 years old. The control group was composed of 24 male, and 33 female participants averaged 40.91 ± 4.4 years old, and no significant difference in age and gender distribution was found between the 2 groups ($P > .05$). The study was carried out following the Helsinki Declaration and authorized by the Medical Ethics Committee of Shangdong Mental Health Center. General materials and clinical information of participants in the disease and control groups were collected and written informed consent was obtained. The study profile is shown in Figure 1.

2.2. Sampling and deoxyribonucleic acid (DNA) extraction

Approximately 5 mL of peripheral venous blood was collected from all participants and fully mixed with an anticoagulant. Mononuclear cells were purified by Percoll, and their genomic DNA was extracted by a DNA extraction kit from Thermo Fisher.

2.3. Polymorphism analysis of rs10767664 and rs7124442 of BDNF gene

The polymorphic region of rs10767664 and rs7124442 site of BDNF gene was amplified by polymerase chain reaction, and the polymorphism of loci of BDNF gene was analyzed by sequencing. Primer used to analyze the polymorphism of rs10767664 and rs7124442 in the BDNF gene was designed on the Primer 3 website (http://primer3.ut.ee/) and synthesized by Shanghai Bioengineering Co., LTD. Primer sequences are listed in Table 1.

2.4. Intestinal flora analysis

Fresh feces (5 g) of participants in the disease and control groups were collected and frozen in a liquid nitrogen tank. Bacterial DNA was extracted from fecal samples by DNA extraction kit following the manufacturer's instructions. Fecal microbiota was analyzed by 16s rRNA next-generation sequencing, and the microbial flora diversity was determined by LefSe analysis. The Chao 1 index was calculated and compared.

2.5. Analysis of inflammatory and immune indexes

Peripheral blood was collected from all participants, and serum was obtained after centrifugation for 10 minutes. The serum concentration of TNF-α, interleukin (IL)-1β, IL-4, IL-10, IgG, and IgM was detected by enzyme-linked immunosorbent assay (BD) following the producer's instructions.

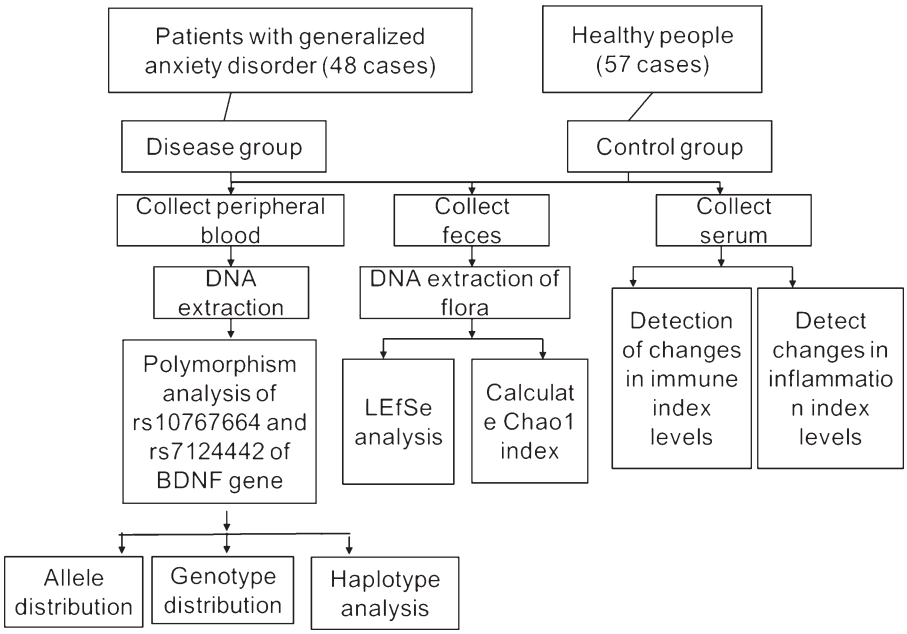

Figure 1. Study profile.

Table 1

Primer sequences.

	Primer type	Primer sequences
rs10767664 site	Sense	TTCCCATCTATTCTTGTCGGG
	Anti-sense	AGGTAGGAGTAACTAGGAAGCT
rs7124442 site	Sense	CCCTTGCAATCCTTTAAGTTTGT
	Anti-sense	AGGAATGCTTGGAATATCTGCT

2.6. Statistical analysis

SPSS 2.0 was used for statistical analysis. The Student *t* test was used to compare quantitative data, and the enumeration data were analyzed by Chi-squared test. Haplotype was estimated with the online program SHEsis. *P* value < .05 was considered statistically significant.

3. Results

3.1. Distribution of rs10767664 and rs7124442 allele of BDNF gene

The distribution of rs10767664 and rs7124442 allele of the BDNF gene is shown in Table 2. A significant difference was observed in the distribution of the rs10767664 allele of the BDNF gene between GAD patients and healthy people (*P* = .004), and the frequency of the T allele in GAD patients was higher.

3.2. Genotype distribution of rs10767664 and rs7124442 of BDNF gene

As shown in Table 3, the genotype distribution of BDNF gene rs10767664 (*P* = .000) and rs7124442 (*P* = .011) in GAD patients were different from those in control group. The frequencies of TT genotype of rs10767664 and CT genotype of rs7124442 of BDNF gene in the disease group were higher than those in the control group.

3.3. Model of rs10767664 and rs7124442 site of BDNF gene

GAD patients showed different distribution of rs10767664 recessive model (*P* = .002) and rs7124442 dominant model (*P* = .040) of BDNF gene with participants in control group (Table 4). The frequency of TT + TA in recessive model of rs10767664 locus of BDNF gene was lower, and the frequency of CC + CT in the dominant model of rs7124442 locus was higher in the disease group.

3.4. Haplotype analysis

As shown in Table 5, the distribution of AC (*P* = .004) and TC (*P* = .019) haplotypes of BDNF gene rs10767664 and rs7124442 sites in GAD patients were different from those in the control group, and the frequency of AC haplotype was lower, whereas the TC haplotype frequency was higher in the disease group.

Table 2

Distribution of rs10767664 and rs7124442 allele of BDNF gene.

Site	Allele	Control group	Disease group	OR value	95% CI	?2	*P*
rs10767664	T	59 (0.518)	68 (0.708)	0.44	0.24-0.78	7.93	.004
	A	55 (0.482)	28 (0.292)				
rs7124442	C	59 (0.518)	49 (0.510)	0.97	0.56-1.67	0.01	.918
	T	55 (0.482)	47 (0.490)				

Table 3

Genotype distribution of rs10767664 and rs7124442 of BDNF gene.

Site	Genotype	Control group	Disease group	?2	*P*
rs10767664	TT	13 (0.228)	28 (0.583)	15.11	.000
	TA	33 (0.579)	12 (0.250)		
	AA	11 (0.193)	8 (0.167)		
rs7124442	CC	17 (0.298)	7 (0.146)	8.98	.011
	CT	25 (0.439)	35 (0.729)		
	TT	15 (0.263)	6 (0.125)		

Table 4

Model of rs10767664 and rs7124442 site of BDNF gene.

	Site	Genotype	Control group	Disease group	?2	*P*
Dominant model	rs10767664	TT+TA	46 (0.807)	40 (0.833)	3.26	.196
		AA	11 (0.193)	8 (0.167)		
	rs7124442	CC+CT	42 (0.737)	42 (0.875)	6.43	.040
		TT	15 (0.263)	6 (0.125)		
Recessive model	rs10767664	TT	13 (0.228)	28 (0.583)	12.13	.002
		TA+AA	44 (0.772)	20 (0.417)		
	rs7124442	CC	17 (0.298)	7 (0.146)	4.25	.119
		CT+TT	40 (0.702)	41 (0.854)		
Heterozygous model	rs10767664	TT	13 (0.228)	28 (0.583)	3.84	.147
		TA	33 (0.579)	12 (0.250)		
	rs7124442	CC	17 (0.298)	7 (0.146)	3.95	.139
		CT	25 (0.439)	35 (0.729)		
Homozygous model	rs10767664	TT	13 (0.228)	28 (0.583)	2.31	.315
		AA	11 (0.193)	8 (0.167)		
	rs7124442	CC	17 (0.298)	7 (0.146)	3.92	.141
		TT	15 (0.263)	6 (0.125)		

Table 5

Haplotype analysis of rs10767664 and rs7124442 sites of BDNF gene.

Haplotype	Control group	Disease group	OR value	95%CI	?2	*P*
AC	30.64 (0.269)	10.53 (0.110)	0.335	0.156~0.719	8.362	.004
AT	24.36 (0.214)	17.47 (0.182)	0.818	0.412~1.624	0.33	.566
TC	28.36 (0.249)	38.47 (0.401)	2.019	1.120~3.638	5.542	.019
TT	30.64 (0.269)	29.53 (0.308)	1.209	0.664~2.202	0.386	.535

Table 6

Comparation of inflammatory levels between disease group and control group (ng/L).

	n	TNF-a	IL-1ß	IL-4	IL-10
Control group	57	8.13 ± 1.30	7.24 ± 0.69	8.84 ± 0.92	4.83 ± 0.38
Disease group	48	18.24 ± 1.74	7.01 ± 1.24	17.62 ± 1.63	5.22 ± 0.27
t		21.24	2.91	18.42	7.28
P		.000	.438	.000	.043

Table 7

Difference in immunity level between disease and control group (U/mL).

	n	IgG	IgM
Control group	57	64.35 ± 4.39	43.35 ± 3.84
Disease group	48	89.24 ± 8.47	45.39 ± 5.40
t		9.34	3.82
P		.008	.277

3.5. Comparison of inflammatory levels between disease group and control group

The levels of TNF-α (P = .000), IL-4 (P = .000), IL-10 (P = .043), and IgG (P = .008) in GAD patients were significantly different from those in the control group, and the overall inflammatory immune level of disease group was higher compared to the control group as shown in Tables 6 and 7.

3.6. Comparison of intestinal flora composition between control and disease group

The abundance of *Paraprevotella*, *Euryarchaeota*, *Caldivirga*, *Porphyromonadaceae*, and *Desulfovibrionales* was higher in GAD patients than in the control group. However, the *Lactobacillus*, *Vagococcus*, *Paludibacter,* and *Barnesiella* were more abundant in the control than in the disease group, as shown in Figures 2 and 3.

3.7. Correlational analysis of microbiota

As depicted in Figure 4, there was a high positive correlation between *Bifidobacterium* and *Rumen cocci* (P = .002, r = 0.44), and a high negative correlation with *Escherichia coli* (P = .000, r = –0.62). At the same time, *E coli* and *Bacteroides* were positively correlated (P = .032, r = 0.26).

3.8. Comparison of intestinal flora diversity between disease and control group

As shown in Figure 5, the Chao1 index representing intestinal flora diversity is significantly lower in the disease group than in the control group (P < .05).

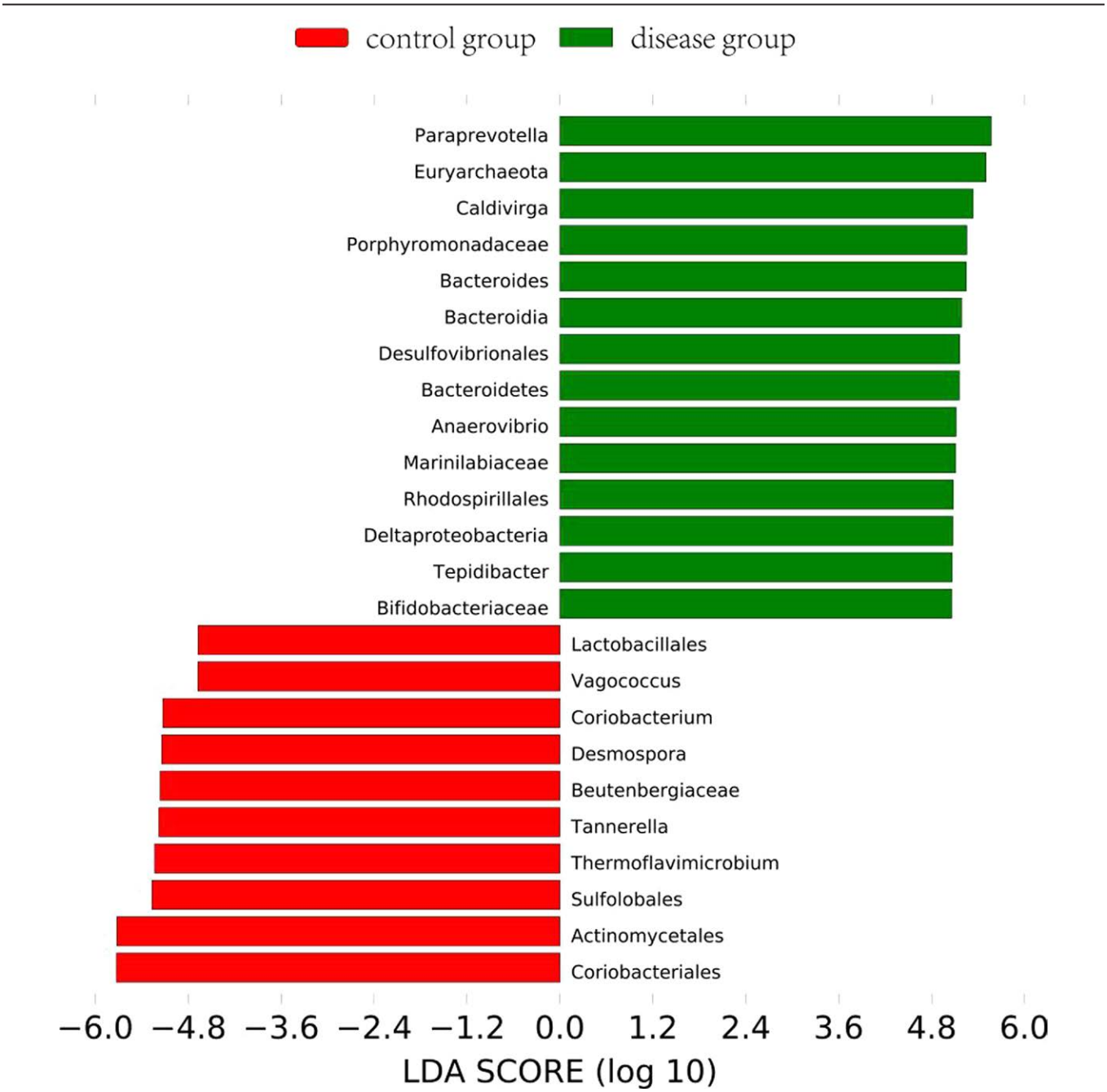

Figure 2. LDA score of microbiota of control and disease group.

4. Discussion

GAD patients suffer from different levels of plant nerve dysfunction, and based on that; they display overstrain and excessive anxiety.[17] GAD is a chronic disease with a longer course, and the patients' conditions worsen if no effective treatment is performed.[18,19] The diagnosis rate of GAD is low worldwide, which might be attributed to the less attention it receives from the public.[20] GAD has a closer relationship with genetic factors.[21] Previous research proved that the occurrence of GAD is related to the polymorphism of several genes, such as rs4680 of catechol-O-methyltransferase gene,[22] C677T of methylenetetrahydrofolate reductase gene[23] rs324981 of NPSR1 gene.[24] These studies indicated that alteration of gene polymorphism might play an important role in the development of GAD. Therefore, a deep understanding of the relationship between gene polymorphism and GAD development is important for elucidating the mechanism of this disease. Meanwhile, discovering more GAD-related polymorphism genes is beneficial to GAD prevention and screening susceptible populations.

BDNF is a neurotrophin vital for the restoration and regeneration of neurologic function.[25] BDNF functions through targeting and binding to its receptor after being released. Its polymorphism is a critical susceptibility factor associated with diseases, especially nerve system diseases.[26] According to previous reports, BDNF gene polymorphism is relevant to the occurrence of many diseases, including major depressive disorder[27] and bipolar disorder.[28] In our study, we compared the difference between rs10767664 and rs7124442 polymorphism of BDNF gene between 48 GAD patients and 57 healthy people and found that the distribution of rs10767664 allele of BDNF gene in GAD patients was significantly different from that in the control group and the frequency of T allele in GAD patients was higher. The genotype distribution of the rs10767664 and rs7124442 sites of the BDNF gene in GAD patients was different from those in the control group. The frequencies of TT genotype and CT genotype of rs10767664 and rs7124442 of the BDNF gene in the disease group were higher than those in the control group. The distribution of rs10767664 recessive model and rs7124442 dominant model of BDNF gene in GAD patients were different from those in the control group. The frequency of TT + TA in the recessive model of rs10767664 locus of BDNF gene was lower than that of CC + CT of rs7124442 dominant locus model in the disease group. The distribution of AC and TC haplotypes of BDNF gene rs10767664 and rs7124442 sites in patients with generalized anxiety disorder were different from those in the control group, and the frequency of AC haplotype was lower, and TC haplotype frequency was higher in the disease group compared to the control group. These results suggested that BDNF gene polymorphism is related to the oncome of GAD, and it modulates the disease in certain ways. Meanwhile, these data also provide important support for screening the potential susceptible populations of GAD and making early intervention measures for the highly susceptible people. Body checks should be taken regularly by people with certain genotypes in rs10767664 and rs7124442 site of BDNF gene, which would reduce the severity of GAD through early diagnosis and treatment.

Intestinal flora is the sum of various microorganisms that reside in the digestive tract, consisting of enormous species and number of bacteria groups.[29,30] Intestinal flora is involved in various physiology and pathology

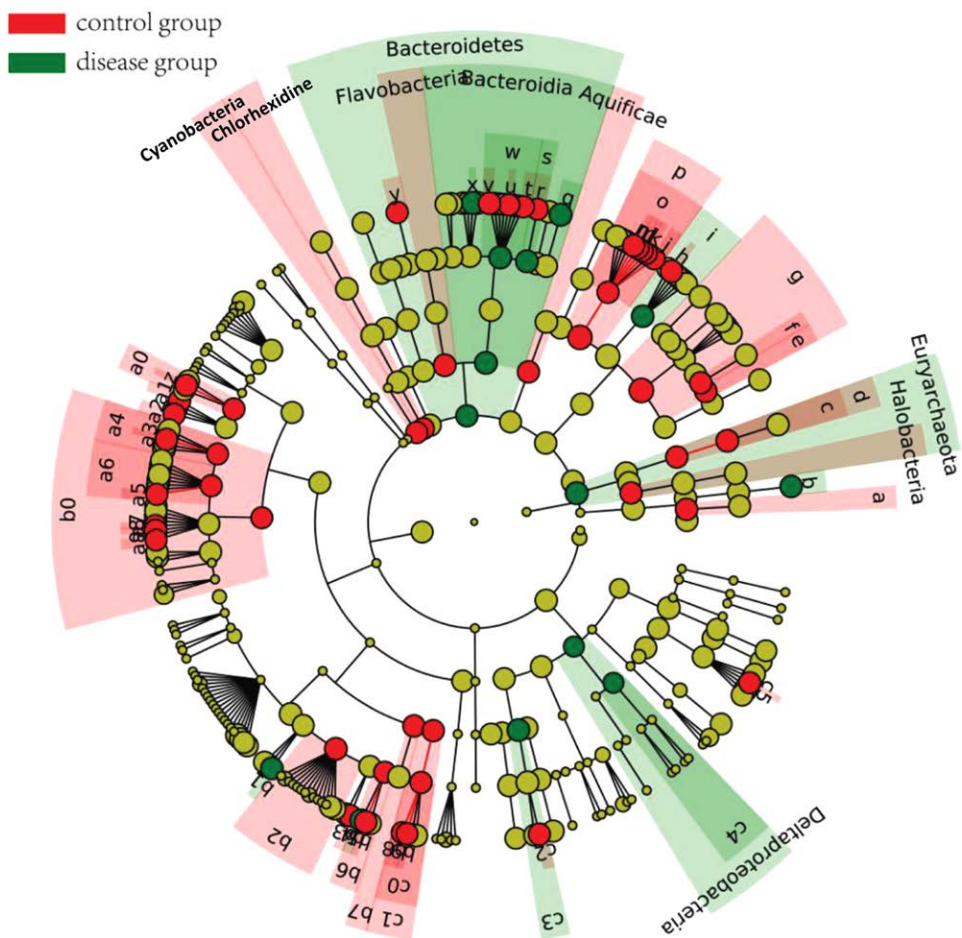

Figure 3. LefSe analysis of control and disease group.

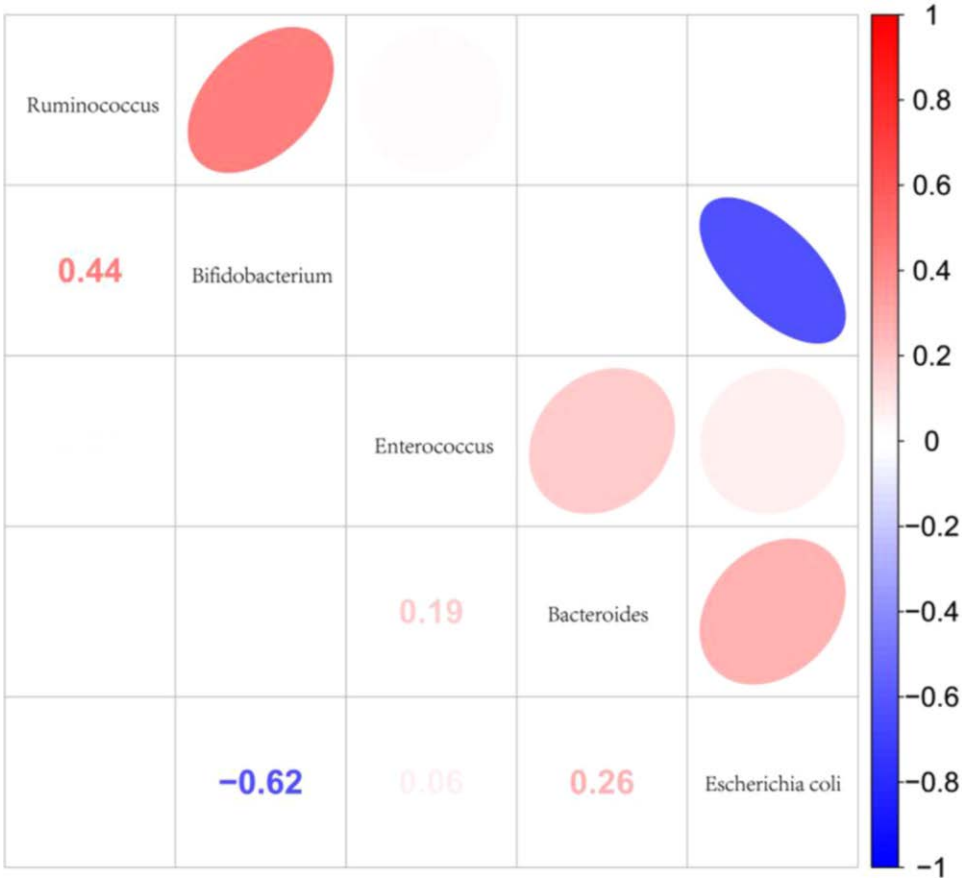

Figure 4. Pearson correlation analysis of microbiota.

processes, such as modulating inflammatory responses, changing the immune status, and influencing the progression of tumors.[31,32] By comparing the microbiota of 48 GAD patients and 57 healthy humans, we found the abundance of *Paraprevotella, Euryarchaeota, Caldivirga, Porphyromonadaceae,* and *Desulfovibrionales* in GAD patients than the control groups. However, abundant *Lactobacillus, Vagococcus, Paludibacter,* and *Barnesiella* were reported in the control group compared to the disease group. *Bifidobacterium* has a high positive correlation with *Rumen cocci*, and a high negative correlation with *E coli* (P = .000, r = –0.62). Meanwhile, *E coli* is positively correlated with *Bacteroides*. The Chao1 index, which symbolizes intestinal flora diversity, was significantly lower in the disease group than in the control group. These results indicated that the composition of intestinal flora in GAD patients is significantly different from that in healthy humans, and it might be the leading cause of GAD. The remarkable change in the abundance of some microbial species might promote the progression of GAD. Inhibitors of the corresponding species or probiotics might modulate the distribution of microbiota in patients and indirectly suppress GAD's development. The shortcoming of this study is that we included 48 GAD patients and 57 healthy humans because of the condition limitations, and the insufficiency of research objects might be an obstacle to the accuracy of results and conclusions. However, our research can still provide new directions for the following explorations and provide a theoretical basis for investigating GAD's pathogenesis.

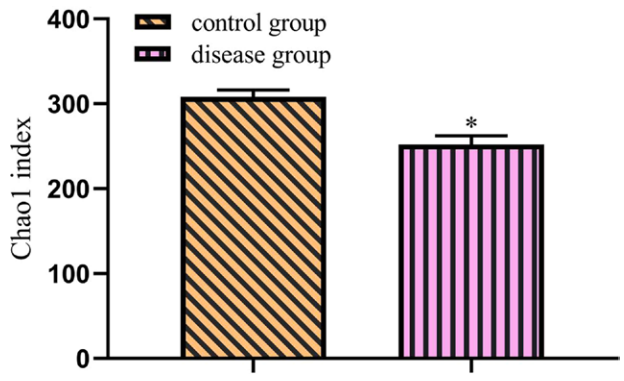

Figure 5. Comparation of intestinal flora diversity between disease group and control group (*P < .05).

5. Conclusion

In conclusion, BDNF gene rs10767664 and rs7124442 polymorphisms are associated with the pathogenesis of GAD, which is accompanied by the increased abundance of *Paraprevotella, Euryarchaeota, Caldivirga, Porphyromonadaceae,* and *Desulfovibrionales*, and the reduced abundance of *Lactobacillus, Vagococcus, Paludibacter*, and *Barnesiella*, as well as the elevated inflammatory immune status.

Author contributions

Study concept and design: YC; analysis and interpretation of data: YW; drafting of the manuscript: WZ and YB; critical revision of the manuscript for important intellectual content: YC and JL; statistical analysis: YW.

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