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Clinical characteristics and differential gene expression analysis of chronic fatigue syndrome with sleep disorder

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Abstract. Objective Preliminary study of clinical features and differential gene expression in chronic fatigue syndrome with sleep disorders. **Methods** Healthy people, chronic fatigue, and CFS patients were included. The FS-14 Scale, PSQI Scale, and MoCA Scale were used to assess fatigue, sleep quality, and cognitive function. The Chronic Fatigue Syndrome targets were searched through the GEO database, and the sleep disorder targets were screened through the GeneBank, Genecards, CTD, and Disgenet databases. Cross-targets were analyzed for GO and KEGG enrichment. **Results** On the comparison of the degree of fatigue and sleep disorder, the CFS patients were more severe than the healthy group and the chronic fatigue group (P<0.01), and the chronic fatigue group was also more severe than the healthy group (P<0.01). On the comparison of cognitive function, CFS patients were more severe than the healthy group and chronic fatigue group (P<0.01), and there was no difference between the chronic fatigue group and the healthy group. Screening obtained 854 CFS disease targets and 3228 sleep disorder targets, totaling 172 cross-targets. **Conclusion** Patients with CFS have significant sleep disturbances and cognitive dysfunction, and fatigue may exacerbate cognitive dysfunction with prolonged disease duration. Mechanisms may be related to pathways of neurodegeneration-multiple diseases, lipid and atherosclerosis, Alzheimer's disease, circadian entrainment, etc., and regulated by pathways such as the cAMP signaling pathway, calcium signaling pathway, and other pathways. This study provides a research basis for exploring the mechanisms of CFS brain function disorders.

Keywords: Chronic fatigue syndrome; Sleep disorder; Differential gene analysis

1. Introduction

Chronic fatigue syndrome (CFS) clinically manifests as severe fatigue that cannot be relieved for a long period, and with the prolongation of the course of the disease as well as the continuous aggravation of the symptoms, accompanied by extensive sleep disorders, as well as central nervous system symptoms such as anxiety and depression, cognitive dysfunction, etc[1]. In clinical practice, the emergence of sleep disorders is frequently a critical time point for the exacerbation of CFS[2]. Therefore, In this study, we preliminarily investigated the clinical characteristics of the evolution of the disease course in CFS patients by scoring their symptoms on a symptomatic scale. In addition, we analyzed the differential gene expression of CFS with sleep disorders and the expression of its related pathways, to provide a

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research basis for the evolution of CFS clinical features and a basis for the staged diagnosis and treatment of CFS prevention and treatment.

2. Methods

2.1. Clinical Cases

The diagnosis of CFS is based on the UK National Institute of Health and Clinical Excellence (NICE) in 2021[3]. The CFS group met the diagnostic criteria of CFS; aged between 18 and 60 years old (including 18 and 60 years old); all of them were initially diagnosed without any clinical diagnostic intervention; voluntarily enrolled in the clinical trial, obeyed the trial arrangement, cooperated with the examination and follow-up, and signed an informed consent form. The healthy group had no history of fatigue or fatigue for less than 3 months and FS-14 score $\leqslant$ 3. The chronic fatigue group had fatigue as the main complaint, with fatigue persisting or recurring for more than 3 months and less than 6 months; the FS-14 score > 3, and the rest were the same as the CFS group. Subjects were screened to exclude other causes of fatigue, musculoskeletal disorders, circulatory disorders, respiratory disorders, and endocrine disorders (e.g., thyroid disorders and diabetes)

A total of 60 subjects were included in this study, including 15 in the healthy group, 15 in the chronic fatigue group, and 30 in the CFS group.

2.2. Symptom scores of CFS patients

The Fatigue Scale-14 (FS-14) developed by Chalder was used, which reflects physical and mental fatigue, with higher scores indicating higher levels of fatigue. The Pittsburgh Sleep Quality Index (PSQI) is a commonly used scale for clinical assessment of sleep quality. It is scored according to 7 items, including sleep quality, time to sleep, sleep duration, sleep efficiency, sleep disorders, hypnotic drugs, and daytime dysfunction, with higher scores indicating poorer sleep quality. The Montreal Cognitive Assessment Scale (MoCA) was used. The scale was assessed in eight cognitive domains (including attention and concentration, executive function, memory, language, visual structural skills, abstract thinking, computation, and orientation). Higher scores indicate better cognitive function.

2.3. Gene acquisition for CFS with sleep disorder

The NCBI GEO database (https://www.ncbi.nlm.nih.gov/geo/) was used to search the corresponding gene expression datasets using the keyword "chronic fatigue syndrome", and the GSE14577 database was selected for the analysis [4]. The probe expression matrix and the annotation file of the platform were downloaded from the GEO database, matched with the probe number and gene symbol, and then filtered by DEGs using R. The filtering condition was $|\log_2 FC|>0.263$, and the CFS differential genes were obtained.

GeneBank (https://www.ncbi.nlm.nih.gov/genbank/), Genecards (https://www.genecards.org/), CTD (https://ctdbase.org/), Disgenet (https://www.disgenet.org/) were used to collect sleep disorder disease targets with "insomnia" as the keyword. The CFS disease targets and sleep disorder disease targets were merged to obtain the CFS with sleep disorder disease targets. The CFS disease targets and sleep disorder disease targets were taken into concatenation and de-emphasized, and the CFS with sleep disorder disease targets were obtained by correcting the gene names through the Uniport (https://www.uniprot.org/) human gene library.

2.4. Enrichment analysis

CFS with sleep disorder targets were imported into the DAVID website (https://david.ncifcrf.gov/) for GO and KEGG pathway enrichment analysis.

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3. Results

3.1. Symptom scores

The FS-14 fatigue score was significantly lower in both the healthy and chronic fatigue groups than that in the CFS group ($P < 0.01$), and fatigue was significantly higher in the chronic fatigue group than that in the healthy group ($P < 0.01$). Sleep quality was significantly better in the healthy group than than in the chronic fatigue group ($P < 0.01$), and sleep quality was significantly lower in the CFS group than in the healthy and chronic fatigue groups ($P < 0.01$). The cognitive function score in both the healthy and chronic fatigue groups were significantly higher than those in the CFS group ($P < 0.01$), indicating cognitive decline in CFS patients. (Table 1).

Table 1. Comparison of symptom scores

Scales	Normal	Chronic fatigue	CFS
FS-14	1.4 ± 0.32^{B}	5.5 ± 1.15^{A}	9.5 ± 2.83^{AB}
PSQI	3.8 ± 1.39^{B}	7.4 ± 1.55^{A}	9.3 ± 2.75^{AB}
MoCA	29.8 ± 0.47	29.2 ± 0.97	27.5 ± 1.38^{AB}

Notes: comparison with normal group, $^{a}P<0.05$, $^{A}P<0.01$; comparison with chronic fatigue group, $^{b}P<0.05$, $^{B}P<0.01$

3.2. CFS with Sleep Disorder Gene Targets

A total of 854 CFS disease targets were obtained from the two platforms of the GSE14577 database, and the differential gene volcano map is shown in Figure 1-2. 3228 sleep disorder genes were obtained, and the two sets of data were taken as a concatenated set, resulting in a total of 172 destination targets. (Figure 3).

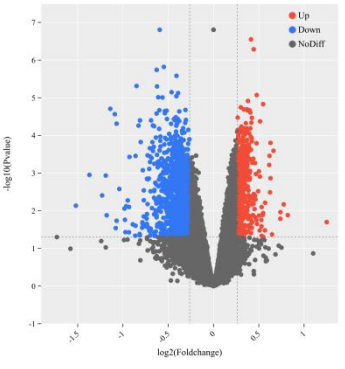

Figure 1. GPL96 Volcano Map

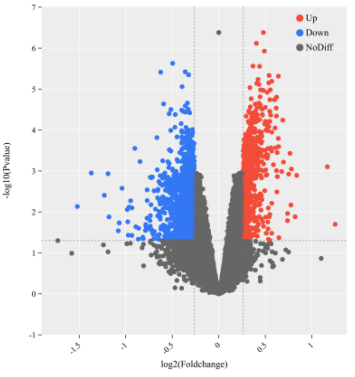

Figure 2. GPL97 Volcano Map

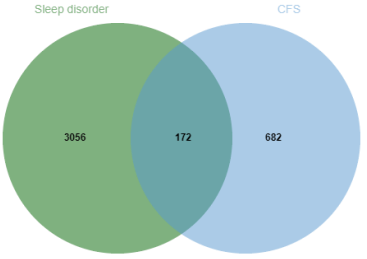

Figure 3. Wayne diagram of intersecting genes

3.3. Enrichment analysis results

The 172 targets were imported into the DAVID database for GO function and KEGG signaling pathway enrichment analysis, and the difference was considered statistically significant at $P<0.01$. The top 3

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highest-ranked enrichments for BP analysis were regulation of cell adhesion, protein phosphorylation, response to hypoxia; the top 3 items in CC analysis were cytoplasm, cytosol, and perinuclear region of cytoplasm; and the top 3 items in MF analysis were RNA binding, protein binding, and kinase activity; the top 10 significant processes in BP, CC, and MF were selected to plot GO functional enrichment maps. (Figure 4). For KEGG enrichment, the most significant 5 processes in each category were selected and plotted as pathway enrichment. (Figure 5).

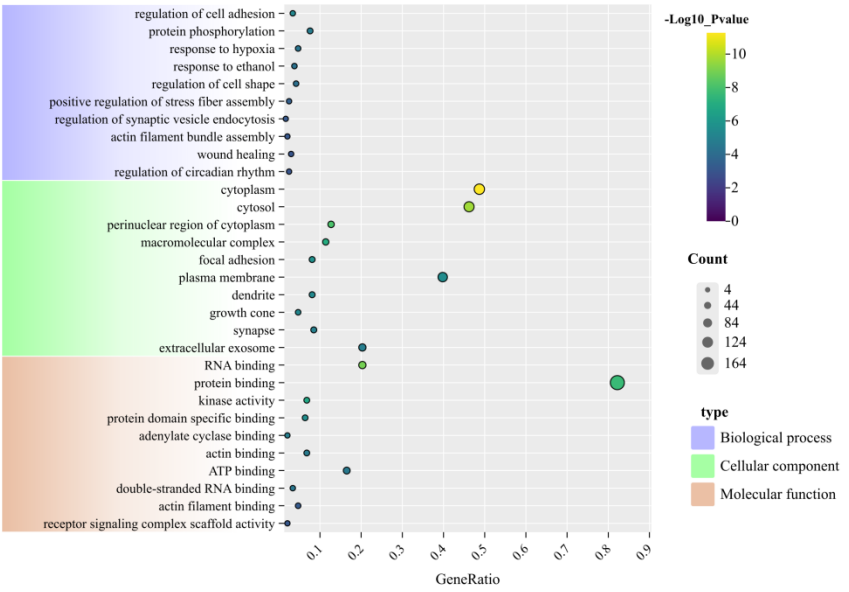

Figure 4. GO Function Enrichment Map

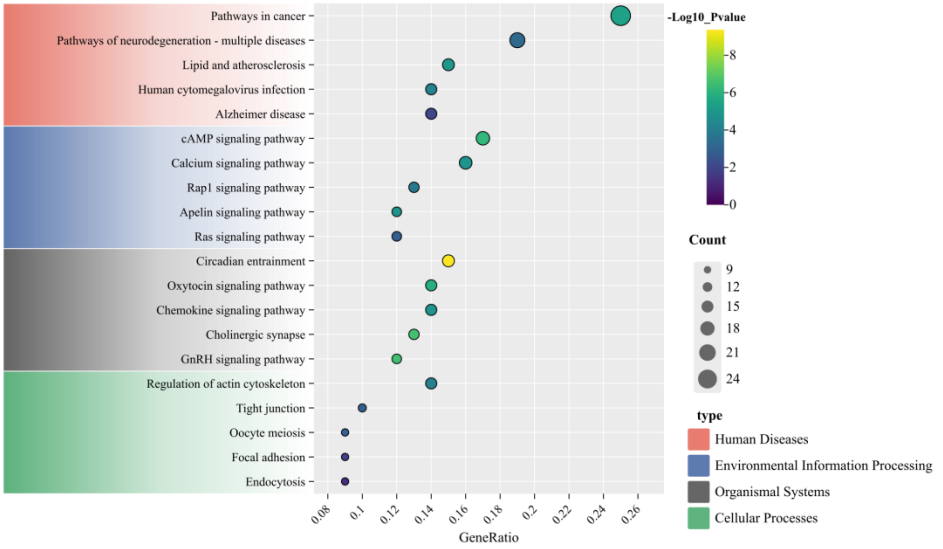

Figure 5. KEGG pathway enrichment map

4. Discussion

CFS has a long course, generally more than half a year of fatigue and accompanying symptoms can not be relieved, in the process of repeated episodes, the body's ability to self-recovery decreases, and its clinical symptoms continue to worsen and lead to further decline in the functioning of various systems,

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and there is now more and more clinical evidence that cognitive impairment and other neurological symptoms seriously impaired the quality of life of patients with CFS [5].

It has been noted that 91% of CFS patients are accompanied by symptoms of sleep disorders [6], and the prevalence of insomnia in CFS patients is double that of the healthy population [7]. Another study found that patients with CFS have altered brain function and impaired neural signaling in the brain, resulting in reduced attention, memory, cognitive impairment, and decreased sleep quality [8]. In this study, we counted symptom scores in healthy people, people with chronic fatigue, and people with CFS, it was found that the chronic fatigue patients with a shorter course than CFS had significantly lower fatigue than the CFS group, and better sleep quality than the CFS group, but there was still a significant difference from the healthy group, at which time there was a tendency to decline in physical strength and sleep, however, there was no significant difference in the cognitive function scores compared with the healthy group. When the disease progressed to the CFS stage, there was a significant decline in cognitive function.

In the KEGG pathway enrichment analysis, we can find significant enrichment in neurodegenerative diseases, Alzheimer's disease, circadian entrainment, and other related CNS diseases. This is consistent with the results of cognitive impairment found in the previous part of the clinical study, suggesting the presence of CNS lesions in CFS. It also provides strategies and ideas for clinical prevention and treatment of CFS, which should be intervened early to try to avoid prolonging the disease and delaying the accompanying symptoms.

CFS involves multi-system lesions and has a complex etiology, commonly involving genetics, viral infections, neuroendocrine immunological abnormalities, central nervous system lesions, HPA axis abnormalities, etc [9]. The screening of biological markers for CFS has been a difficult task for academics. The microarray dataset included in this study was screened for differential genes with a multiplicity of variance of 1.2, which may not be extremely significant differential genes, but we were able to screen for more effective genes for prediction under these conditions, which may only provide a referenceable research direction for the disease, and future studies will still need to identify other specific indicators of altered sleep characteristics in CFS patients [10]. Great thanks to Prof. Suzanne Hagan et al. at Glasgow Caledonian University for providing publicly available data.

5. Conclusion

In this study, we analyzed the clinical symptoms of CFS patients.We found the clinical features that the severity of sleep disorder and cognitive impairment aggravated with the prolongation of the disease. We also analyzed the disease targets of CFS combined with sleep disorder and found the potential mechanism of neurodegenerative changes, which provides a research basis for exploring the mechanism of CFS brain function disorders.

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