COMMENTARY ARTICLE

Comprehensive microarray analysis of downregulation of three immune-specific core genes and regulatory pathways in children and adults with friedreich's ataxia

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ABSTRACT

Friedreich's Ataxia (FRDA) is a hereditary illness for which there is no treatment. As a result, new biomarkers and essential mechanisms connected to FRDA advancement must be discovered as soon as possible. Friedreich's Ataxia (FRDA) is a genetic spinal cord and cerebellar condition caused mostly by homozygous repetitive amplification of the Guanine-Adenine-Adenine (GAA) triplet in the frataxin gene. The expression level of functional Frataxin decreases as a result of repeat amplification and mutation. Frataxin deficiency can cause mitochondrial dysregulation by promoting the activation of oxidative stress and ferroptosis. Initial symptoms in children frequently include a loss of balance and increasing ataxia. Patients may develop dysarthria and loss of tendon reflex as the condition progresses, and in many cases, this is followed by myocardial infarction and diabetes. There is currently no effective therapy for preventing FRDA progression, with the majority of treatments being symptomatic. As a result, a greater understanding of the underlying pathophysiology and the development of more effective treatment techniques is critical. Some serum biomarkers have recently been identified as possible essential signatures in the aetiology of FRDA. The levels of neurofilament light and heavy chains, for example, are markedly elevated in Friedreich's ataxia patients and decline with age. Furthermore, serum hsTnT, NT-proBNP, and miRNAs have been linked to the advancement of cardiomyopathy in adult FRDA patients. However, the clinical use of these biomarkers has yet to be proven in prospective cohorts, and the clinical association between them is poorly understood. Furthermore, these biomarkers have yet to be employed in FRDA clinical diagnosis. As a result, identifying additional biomarkers could provide crucial information on FRDA diagnosis and treatment. Bioinformatics analysis is currently being used to find critical biomarkers closely connected to disease prognosis in a range of disorders, including cancer, cardiac disease, and neurodegenerative disease. Furthermore, competitive endogenous RNA (ceRNA) networks will aid in the understanding of the novel mechanism of transcriptional regulatory networks in disease progression.

Key Words: *Friedreich's ataxia; Biomarker; Hub genes; Bioinformatics; RNA*

INTRODUCTION

Only a few studies have looked at the relationship between Differentially Expressed Genes (DEGs) in children and adult FRDA, despite recent research focusing on FRDA-induced transcriptome modifications. By intersecting the up-regulated and down-regulated DEGs in child and adult FRDA data, we discovered Co-Expressed Differentially Expressed Genes (co-DEGs). Then, using multiple enrichment analyses and a PPI network, we were able to identify the major pathways and hub genes associated with the progression of FRDA in children and adults. Using the GSE30933 dataset, we also identified hub gene target miRNAs and confirmed the diagnostic importance of chosen hub genes. Finally, we built FRDA-related ceRNA networks based on interactions between mRNAs, miRNAs, and long noncoding RNAs (lncRNAs) [1]. Our research offers a fresh look at the pathophysiology of FRDA progression at the transcriptome level, as well as prospective targets for the diagnosis and therapy of FRDA in both children and adults.

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Immune infiltration analysis and gsea

To better understand the biological process and immune cell subtype involved in the child and adult samples, we used GSEA to find that the genes in children were significantly enriched in antigen-receptor mediated signalling, defence response to virus, NF-B signalling, regulation of immune response signalling pathways, and T cell receptor signalling pathways [2]. In adults, the enriched gene sets were mostly involved in virus defence, T cell differentiation regulation, interferon-gamma response, virus response, and viral gene expression. Following that, we used immune infiltration analysis to discover that the proportions of immune cell subtypes were different between groups. The FRDA children group had a higher number of resting memory CD4+ T cells and Neutrophils than the Control children group. In addition, when compared to the Control adult group, the FRDA adult group significantly increased the number of CD8+ T cells and activated NK cells, while the number of memory B cells, resting memory CD4+ T cells, activated memory CD4+ T cells, M1 Macrophages, resting Dendritic cells, activated Dendritic cells, and resting Mast cells decreased [3].

Functional Enrichment Analysis and Co-DEG Identification

When the DEGs from the child and adult datasets were combined, 29 co-up-regulated and 59 co-down-regulated DEGs were discovered. To learn more about the enrichment pathways involved in these co-DEGs, we used the DAVID website to do GO enrichment analysis. The immune effector process, virus defence, immune system process, defence response to other species, and hemopoiesis were all biological processes that these co-DEGs were involved in. Furthermore, KEGG pathway enrichment analysis revealed that these co-DEGs were primarily engaged in IgA production, autoimmune thyroid disease, measles, lysosome, necroptosis, and influenza A in the intestinal immune network. These co-DEGs were largely enriched in the immune system, inflammatory reaction, necrosis, and signal transduction, according to reactome enrichment analysis. In both the kid and adult datasets, we perform immune infiltration analyses of co-DEGs. In different groups, the proportions of immune cell subtypes were clearly visible. In the FRDA children group, the number of Plasma cells, M0 Macrophages, and Neutrophils grew greatly, but the number of resting memory CD4+ T cells, active memory CD4+ T cells, Monocytes, M1 Macrophages, and M2 Macrophages decreased dramatically. When compared to the Control adult group, the FRDA adult group significantly increased the amount of naive B cells, Plasma cells, M0 Macrophages, and Neutrophils, while significantly decreasing the number of naive T cells CD4, M1 Macrophages, M2 Macrophages, and resting Mast cells [4].

Hub genes identification, ppi network and cluster modules analysis
The STRING website was used to build the PPI network of co-DEGs, which included 45 nodes and 56 edges, and Cytoscape software was used to view it. Using the MCODE plugin, we then filtered out a cluster module containing six down-regulated genes (Figure 5B). The findings of five algorithms from the cytoHubba plugin (Degree, MNC, Closeness, Stress, and Radiality) were then intersected to identify a total of ten hub genes [5]. All of the identified hub genes were considerably down-regulated in FRDA samples, and they were mostly involved in immune system processes and responses to other species. These findings show that decreased expression of these hub genes plays a significant role in the pathophysiology of FRDA [6].

Target miRNAs mining, interaction network construction, and target mirna functional enrichment analysis

By binding the 3'UTR of mRNAs, miRNAs serve a critical role in promoting gene degradation, acting as a negative regulator. We found 150 target miRNAs for eight identified hub genes, as well as 156 mRNA-miRNA pairings. Furthermore, using the Cytoscape software, an mRNA-miRNA interaction network with 158 nodes and 156 edges was created and shown based on the prediction results. The miRNAs with the most cross-linked genes (two) were discovered. Furthermore, miRNA functional analysis revealed that protein serine/threonine kinase activity, transcription factor activity, GTPase activity, ubiquitin-specific protease activity, receptor binding, and receptor signalling protein serine/threonine kinase activity were markedly enriched in molecular functions [7]. The glypican pathway, syndecan-1-mediated signalling, proteoglycan syndecan-mediated signalling, IFN-gamma route, ErbB receptor signalling, and c-Met-mediated signalling were the key biological pathways involved. LncRNAs, as upstream molecules of miRNAs, have the potential to control miRNA biological function. As a result, we predicted the miRNAs' target lncRNAs for the CD28, FAS, and IFIT5 genes. The CD28-miRNA interaction network yielded 5 target lncRNAs, while the FAS-miRNA and IFIT5-miRNA interaction networks yielded 3 and 12 target lncRNAs, respectively. Cytoscape software was used to create three ceRNA networks, which were then displayed. Following that, we conducted a literature search and discovered that miR-24-3p had only been documented in FRDA. As a result, we hypothesised that NEAT1-hsa-miR-24-3p-CD28 is a possible RNA regulatory mechanism implicated in the progression of FRDA in children and adults.

DISCUSSION

FRDA is an autosomal recessive hereditary disorder that causes damage to many organ systems. Bioinformatics analysis has been widely developed and applied in numerous diseases in recent years, revealing the underlying pathophysiology of disease and identifying important biomarkers for disease diagnosis and prognosis. Despite this, no systematic research on the link between child and adult FRDA based on bioinformatics has been published too far. After intersecting the up-regulated and down-regulated DEGs across the child and adult datasets, 88 co-DEGs were discovered. GSEA and immune infiltration analyses revealed that these genes were primarily enriched in the immune response in both the kid and adult datasets. The immunological response defined by immune cell activation and innate immune response regulation was much greater in FRDA samples, according to GO and KEGG pathway enrichment analyses of co-DEGs. Reactome analysis also demonstrated that immune system activation, necrosis, and signal transduction were all linked to the progression of FRDA in both children and adults. Immune system dysfunction is critical for the prognosis of many disorders, including FRDA. It was recently used bioinformatics to show that there are significant changes in the proportion of Natural Killer (NK) cells across control, carrier, and FRDA groups, and that they are severely diminished in FRDA patients. Furthermore, IL-6, a macrophage-produced cytokine, has been found to be elevated in the blood plasma of FRDA patients, suggesting that macrophage activation may be involved in the neuropathology of FRDA. However, in the FRDA adult group, there was a substantial drop in macrophages and a spectacular rise in activated NK cells; however, there was no statistical significance in the number of natural killer cells and macrophages between the FRDA children and Control children groups. This mismatch could have been

caused by the following facts: For starters, batch effects are created when multiple datasets are used for analysis, which can result in different outcomes. Second, the results may alter depending on whether the subjects are from various locations or ethnicities. We divided FRDA into adult and child categories and looked into the relationship between FRDA and immune cell types in adults and children, which could be another reason for the mixed results. Furthermore, we used the Cibersort algorithm for immune infiltration analysis rather than the quadratic programming method in our work, implying that the impact of different analytic methodologies on the results should not be overlooked.

CONCLUSION

In summary, our study found the downregulation of three immune-specific hub genes, CD28, FAS, and IFIT5, may be associated with the progression of child and adult FRDA. Furthermore, NEAT1-hsa-miR-24-3p-CD28 may be a potential RNA regulatory pathway related to the pathogenesis of child and adult FRDA. These findings provide a novel perspective for exploring the pathophysiological mechanism of FRDA progression at the transcriptome level.

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