

## **Transcriptomic Identification of Mitochondrial Dysfunction Signatures Associated with Ischemic Stroke**

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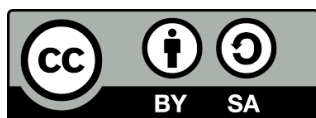
### **Keywords:**

Bioinformatics; Ischemic Stroke;  
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### **ABSTRACT**

Mitochondrial dysfunction contributes to the pathophysiology of ischemic stroke through impaired energy production, oxidative stress, and activation of cell death pathways. This study aimed to identify mitochondria-related transcriptomic signatures associated with ischemic stroke using an integrative bioinformatics approach. The GSE16561 peripheral whole-blood transcriptomic dataset, comprising 39 patients with ischemic stroke and 24 healthy controls, was analyzed to identify differentially expressed genes (DEGs). The identified DEGs were intersected with the MitoCarta3.0 mitochondrial gene set to identify mitochondria-related DEGs. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed to characterize the biological functions and pathways associated with these genes. A protein-protein interaction (PPI) network was subsequently constructed to identify highly connected hub genes. A total of 1,284 DEGs were identified, including 731 upregulated and 553 downregulated genes. Intersection with the MitoCarta3.0 gene set yielded 86 mitochondria-related DEGs, comprising 49 upregulated and 37 downregulated genes. Functional enrichment analyses revealed significant involvement of pathways and biological processes associated with oxidative phosphorylation, mitochondrial respiratory chain activity, ATP metabolism, reactive oxygen species (ROS) metabolism, mitochondrial organization, and apoptotic signaling. PPI network analysis identified NDUFA1, NDUFS2, UQCRC1, COX5A, and ATP5F1A as five major hub genes, suggesting coordinated transcriptional alterations across multiple components of the mitochondrial oxidative phosphorylation system. Overall, ischemic stroke was associated with a distinct mitochondria-related transcriptomic signature characterized primarily by alterations in mitochondrial energy metabolism and respiratory chain function. The identified hub genes represent potential molecular candidates for further investigation into the role of mitochondrial dysfunction in ischemic stroke. However, independent clinical and experimental validation is necessary to establish their biological relevance and potential translational significance.



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## **INTRODUCTION**

Ischemic stroke is a leading cause of mortality and long-term neurological disability worldwide. It occurs when cerebral blood flow is interrupted, resulting in an inadequate

supply of oxygen and metabolic substrates to brain tissue. The resulting ischemic cascade involves rapid disruption of cellular energy homeostasis, excitotoxicity, oxidative stress, inflammation, and activation of cell death pathways (Majumder, 2024; Sudiyono et al., 2026). Although advances in acute reperfusion therapies have improved clinical outcomes, the molecular mechanisms underlying ischemic brain injury remain complex, emphasizing the need for further investigation into the biological pathways involved in stroke pathogenesis (Xu et al., 2025; Pranandi, 2026).

Mitochondria play a central role in cellular responses to cerebral ischemia. In addition to producing adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS), mitochondria regulate reactive oxygen species (ROS) production, calcium homeostasis, metabolic signaling, and apoptosis. Disruption of oxygen and glucose delivery impairs mitochondrial electron transport chain activity and reduces ATP production, while subsequent metabolic disturbances promote excessive ROS generation, oxidative stress, and mitochondrial damage (Liu et al., 2018; Pranandi, 2026b). These alterations can exacerbate cellular injury, impair neuronal function, and contribute to neuronal cell death. Consequently, mitochondrial dysfunction represents a critical mechanism underlying the pathophysiology of ischemic stroke (Huang et al., 2023; Pranandi & Tjhay, 2025).

Transcriptomic analysis provides a systematic approach to investigating disease-associated changes in gene expression and identifying molecular pathways involved in pathological processes. Publicly available gene expression datasets have facilitated the characterization of transcriptional alterations associated with ischemic stroke across various biological samples (Casamassimi et al., 2017; Pranandi & Arieselia, 2026). However, focusing specifically on genes involved in mitochondrial function may provide a more targeted understanding of the relationship between mitochondrial dysfunction and systemic molecular responses to cerebral ischemia. Integrating differential gene expression analysis with curated mitochondrial gene sets, functional enrichment analysis, and protein–protein interaction (PPI) network analysis may help identify mitochondrial genes and biological processes associated with ischemic stroke (Huang et al., 2023; Pranandi, 2025).

This study aimed to identify mitochondria-related transcriptomic signatures associated with ischemic stroke using publicly available gene expression data. Differentially expressed genes (DEGs) identified by comparing patients with ischemic stroke and healthy controls were intersected with a curated mitochondrial gene set to identify mitochondria-related DEGs (Zhao et al., 2026; Pranandi, 2025b). Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were subsequently conducted to characterize the biological functions and molecular pathways associated with these genes. PPI network analysis was also performed to identify highly connected hub genes potentially involved in mitochondrial dysfunction (de Oliveira et al., 2026; Greenblatt et al., 2024). This integrative bioinformatics approach was intended to provide a focused understanding of mitochondrial transcriptional alterations associated with ischemic stroke and identify candidate molecular targets for further investigation.

## **METHOD**

### **Data Source and Study Design**

This study employed a retrospective bioinformatics approach using publicly available transcriptomic data to identify mitochondria-related gene expression signatures associated with ischemic stroke. The GSE16561 dataset was retrieved from the National Center for Biotechnology Information Gene Expression Omnibus (NCBI GEO) database (Clough et al., 2024). The dataset comprised peripheral whole-blood gene expression profiles from 63 participants, including 39 patients with ischemic stroke and 24 neurologically healthy controls. Gene expression profiling was performed using the Illumina HumanRef-8 v3.0 Expression BeadChip platform (Illumina, 2026).

The analytical workflow involved differential gene expression analysis between the ischemic stroke and control groups, followed by the intersection of differentially expressed genes (DEGs) with a curated mitochondrial gene set. The resulting mitochondria-related DEGs were subjected to functional enrichment analysis and protein–protein interaction (PPI) network analysis to identify mitochondrial biological processes and candidate hub genes associated with ischemic stroke (de Oliveira et al., 2026; Greenblatt et al., 2024). As the study exclusively analyzed publicly available, deidentified transcriptomic data, no additional participants were recruited, and no personally identifiable information was accessed.

### **Data Preprocessing and Differential Expression Analysis**

The processed gene expression matrix and corresponding sample information for GSE16561 were obtained from the Gene Expression Omnibus database (Clough et al., 2024). Probe identifiers were mapped to their corresponding official gene symbols according to the platform annotation file. Probes without valid gene annotations were excluded, while multiple probes corresponding to the same gene were summarized by calculating their mean expression value. Expression values were assessed for appropriate transformation and normalization before subsequent analysis.

Differential gene expression analysis was performed by comparing samples from patients with ischemic stroke with those from healthy controls using the limma package in R.19 A linear model was fitted for each gene to estimate differences in expression between the two groups. Multiple testing was controlled using the Benjamini–Hochberg method.20 Genes with an adjusted P value  $<0.05$  and an absolute  $\log_2$  fold change ( $|\log_2\text{FC}|$ )  $>0.5$  were considered differentially expressed. Genes with positive  $\log_2\text{FC}$  values were classified as upregulated, whereas those with negative values were classified as downregulated in ischemic stroke relative to controls (B. Zhao et al., 2018).

### **Identification of Mitochondria-Related Differentially Expressed Genes**

A curated list of human mitochondria-associated genes was obtained from the MitoCarta3.0 database, which provides a comprehensive inventory of genes encoding proteins with established or predicted mitochondrial localization. The human mitochondrial gene set was used as the reference for identifying mitochondrial alterations associated with ischemic stroke (Rath et al., 2021).

The differentially expressed genes identified from the GSE16561 dataset were intersected with the MitoCarta3.0 gene set based on official gene symbols. Genes present in both datasets were defined as mitochondria-related differentially expressed genes (mito-DEGs). These genes were further classified as upregulated or downregulated according to the

direction of expression change in ischemic stroke relative to healthy controls. The resulting mito-DEG set was used for subsequent functional enrichment and protein–protein interaction network analyses (Rath et al., 2021).

### **Functional Enrichment Analysis**

Functional enrichment analysis was performed to characterize the biological processes and pathways associated with the identified mitochondria-related differentially expressed genes. Gene Ontology (GO) (Consortium, 2026) Biological Process and Kyoto Encyclopedia of Genes and Genomes (KEGG)24 pathway enrichment analyses were conducted using the clusterProfiler package in R (Daswito et al., 2023). Official gene symbols were converted to the corresponding Entrez Gene identifiers before enrichment analysis.

Overrepresentation analysis was performed using the identified mito-DEGs as the input gene set. Enriched terms related to mitochondrial function, including energy metabolism, oxidative phosphorylation, respiratory-chain activity, reactive oxygen species metabolism, mitochondrial organization, and cell-death signaling, were examined to characterize the major biological alterations associated with ischemic stroke. Multiple-testing correction was performed using the Benjamini–Hochberg method, and enrichment terms with an adjusted P value <0.05 were considered statistically significant (Palejev & Savov, 2021; B. Zhao et al., 2018).

### **Protein–Protein Interaction Network and Hub Gene Identification**

A protein–protein interaction (PPI) network was constructed to investigate potential functional interactions among the identified mitochondria-related differentially expressed genes.16 The mito-DEGs were submitted to the STRING database, with Homo sapiens selected as the organism. (Szklarczyk et al., 2025) Protein interactions with a combined confidence score  $\geq 0.4$  were retained for network construction, while disconnected nodes were excluded from further network analysis.

The resulting interaction network was imported into Cytoscape for visualization and topological analysis. (Shannon et al., 2003) Node degree was used as the primary measure of network connectivity, with genes exhibiting a greater number of interactions considered more central within the network. Genes were ranked according to their degree values, and the five highest-ranking genes were defined as candidate hub genes. These hub genes were subsequently examined in relation to their mitochondrial functions and potential involvement in the molecular mechanisms associated with ischemic stroke.

### **Statistical Analysis**

All statistical analyses were performed using R software. (Shannon et al., 2003) Differential gene expression between the ischemic stroke and healthy control groups was assessed using linear modeling implemented in the limma package. Multiple comparisons were adjusted using the Benjamini–Hochberg method to control the false discovery rate. Genes with an adjusted P value <0.05 and  $|\log_2\text{FC}| > 0.5$  were considered differentially expressed.

For functional enrichment analysis, GO Biological Process and KEGG pathway terms with an adjusted P value <0.05 were considered statistically significant. (Laboratories, 2026; Consortium, 2026) Protein–protein interaction network connectivity was evaluated using node degree, and the five genes with the highest degree values were designated as candidate

hub genes.<sup>16</sup> All statistical tests were two-sided where applicable, and an adjusted P value <0.05 was considered statistically significant.

## RESULTS AND DISCUSSION

### Characteristics of the Transcriptomic Dataset

The GSE16561 transcriptomic dataset was used to investigate gene expression alterations associated with ischemic stroke. The dataset comprised 63 peripheral whole-blood samples, including 39 samples from patients with ischemic stroke and 24 samples from neurologically healthy controls. All samples were derived from *Homo sapiens* and profiled using the Illumina HumanRef-8 v3.0 Expression BeadChip platform. The characteristics of the dataset included in the analysis are summarized in Table 1.

**Table 1.** Characteristics of the transcriptomic dataset included in the study

| Characteristic      | Ischemic stroke                                 | Healthy control                                 |
|---------------------|-------------------------------------------------|-------------------------------------------------|
| GEO accession       | GSE16561                                        | GSE16561                                        |
| Number of samples   | 39                                              | 24                                              |
| Total sample size   |                                                 | 63                                              |
| Organism            | <i>Homo sapiens</i>                             | <i>Homo sapiens</i>                             |
| Sample source       | Peripheral whole blood                          | Peripheral whole blood                          |
| Expression platform | Illumina HumanRef-8 v3.0<br>Expression BeadChip | Illumina HumanRef-8 v3.0<br>Expression BeadChip |
| Data type           | Gene expression microarray                      | Gene expression microarray                      |

Following preprocessing and gene annotation, the expression profiles were organized according to ischemic stroke and healthy control status for subsequent differential expression analysis. The resulting dataset provided the basis for identifying stroke-associated transcriptional alterations and determining the subset of differentially expressed genes associated with mitochondrial function.

### Differentially Expressed and Mitochondria-Related Genes

Differential gene expression analysis revealed substantial transcriptional differences between patients with ischemic stroke and healthy controls.<sup>27</sup> Using an adjusted P value <0.05 and  $|\log_2\text{FC}| > 0.5$  as the significance thresholds, a total of 1,284 differentially expressed genes (DEGs) were identified. Among these, 731 genes were upregulated and 553 genes were downregulated in the ischemic stroke group relative to the healthy control group.

To specifically characterize mitochondrial alterations associated with ischemic stroke, the 1,284 DEGs were intersected with the curated human mitochondrial gene set obtained from MitoCarta3.0.<sup>22</sup> This analysis identified 86 mitochondria-related differentially expressed genes (mito-DEGs). Of these, 49 were upregulated and 37 were downregulated in ischemic stroke.

Overall, mitochondria-related genes accounted for approximately 6.7% of all identified DEGs, indicating that a distinct subset of the transcriptional alterations observed in ischemic stroke involved genes associated with mitochondrial function. These 86 mito-DEGs were subsequently used for functional enrichment and protein–protein interaction network analyses to characterize the mitochondrial biological processes and molecular interactions associated with ischemic stroke.

### **Functional Enrichment of Mitochondria-Related Genes**

Functional enrichment analysis of the 86 mitochondria-related differentially expressed genes demonstrated significant involvement of biological processes related to mitochondrial energy production, respiratory-chain activity, oxidative stress, and cellular responses to mitochondrial dysfunction. Gene Ontology Biological Process analysis showed prominent enrichment in oxidative phosphorylation, mitochondrial ATP synthesis, mitochondrial respiratory-chain complex assembly, reactive oxygen species metabolic processes, mitochondrial organization, and regulation of apoptotic signaling (adjusted  $P < 0.05$ ).<sup>11,23</sup>

Consistent with the Gene Ontology findings, KEGG pathway analysis demonstrated significant enrichment of pathways associated with oxidative phosphorylation, thermogenesis, reactive oxygen species-related processes, and apoptosis. Among these findings, oxidative phosphorylation represented one of the most prominent mitochondrial pathways associated with the identified gene set, indicating coordinated alterations in genes involved in cellular energy metabolism.

Collectively, the enrichment profile suggested that mitochondria-related transcriptional alterations in ischemic stroke were predominantly associated with disturbances in mitochondrial energy metabolism and respiratory-chain function, accompanied by changes in oxidative stress and cell-death-related processes. These findings provided the biological basis for subsequent protein–protein interaction analysis to identify highly connected mitochondrial genes potentially contributing to the observed molecular signature.

### **PPI Network and Hub Gene Identification**

Protein–protein interaction analysis was performed to characterize the functional connectivity among the 86 mitochondria-related differentially expressed genes. Following removal of disconnected nodes, the resulting PPI network demonstrated extensive interactions among proteins involved in mitochondrial energy metabolism and respiratory-chain function. A prominent interconnected region was formed by proteins associated with oxidative phosphorylation, supporting the functional enrichment findings described above.

Network topological analysis based on node degree identified NDUFA1, NDUFS2, UQCRC1, COX5A, and ATP5F1A as the five most highly connected genes within the mitochondrial interaction network. These genes encode proteins associated with major components of the mitochondrial oxidative phosphorylation system, including respiratory-chain complexes I, III, and IV and mitochondrial ATP synthase. Their high connectivity suggested that alterations affecting multiple components of mitochondrial energy production contributed to the transcriptomic signature observed in ischemic stroke.

The overall PPI network and the relative connectivity of the identified hub genes are presented in Figure 1. In the network visualization, node size represents connectivity based on degree, allowing highly connected genes to be distinguished from other mitochondria-related differentially expressed genes. The coordinated presence of hub genes across several components of the oxidative phosphorylation machinery further supported mitochondrial energy metabolism as a central feature of the identified ischemic stroke-associated transcriptomic signature (Greenblatt et al., 2024; Sun et al., 2025).



highly connected hub genes. Collectively, these findings suggest that coordinated transcriptional alterations affecting mitochondrial energy metabolism represent an important component of the molecular response associated with ischemic stroke (Saravanan et al., 2022; Clarina et al., 2025).

Mitochondrial energy failure is a central feature of ischemic injury. The brain has a high and continuous demand for energy, while its capacity to maintain energy production during interruption of oxygen and glucose delivery is limited. Cerebral ischemia rapidly compromises oxidative phosphorylation, leading to decreased ATP production and disruption of energy-dependent cellular processes. The enrichment of mitochondrial respiratory-chain and ATP metabolic processes observed in the present analysis is consistent with this biological mechanism. Importantly, the transcriptomic alterations involved multiple components of the oxidative phosphorylation system, suggesting that mitochondrial dysfunction associated with ischemic stroke may reflect coordinated changes across the respiratory machinery rather than alterations in a single molecular pathway (Wen et al., 2025; Goel et al., 2025).

Mitochondrial dysfunction is also closely associated with oxidative stress during ischemic injury. Disturbances in electron transport can promote the generation of reactive oxygen species, which may damage proteins, lipids, nucleic acids, and mitochondrial structures. Excessive oxidative stress may further impair mitochondrial function, creating a cycle of mitochondrial injury and cellular dysfunction. In addition, mitochondria participate in the regulation of apoptotic signaling and other mechanisms of cell death. The observed enrichment of genes involved in reactive oxygen species metabolism, mitochondrial organization, and apoptotic processes therefore suggests that the identified transcriptomic signature extends beyond impaired energy production and may reflect broader mitochondrial stress responses associated with ischemic stroke (Zong et al., 2024; Handayani et al., 2025).

Network analysis further highlighted five candidate hub genes involved in mitochondrial oxidative phosphorylation. NDUFA1 and NDUF52 are components of mitochondrial complex I, which contributes to electron transfer from NADH and the generation of the proton gradient across the inner mitochondrial membrane. UQCRC1 is a component of complex III, whereas COX5A contributes to cytochrome c oxidase activity within complex IV. ATP5F1A encodes a major component of mitochondrial ATP synthase, which utilizes the proton gradient generated by the respiratory chain to produce ATP. The identification of highly connected genes spanning several respiratory-chain complexes supports the concept that mitochondrial alterations in ischemic stroke involve interconnected components of oxidative phosphorylation. These genes may therefore represent useful candidates for further investigation of mitochondrial responses to cerebral ischemia (Gusic & Prokisch, 2021; William et al., 2025).

The use of peripheral whole-blood transcriptomic data also provides a systemic perspective on mitochondrial alterations associated with ischemic stroke. Blood-based gene expression profiles may capture changes related to immune activation, metabolic stress, and other systemic responses occurring after cerebral ischemia. From a translational perspective, genes detectable in peripheral blood may also be more accessible for future biomarker investigations than molecular alterations requiring brain tissue. Nevertheless, the present findings should not be interpreted as direct evidence of mitochondrial dysfunction within

neurons or other brain cells. Rather, they represent circulating transcriptomic changes associated with ischemic stroke that are enriched for genes involved in mitochondrial biology (Mu et al., 2026).

Several limitations should be considered. First, the analysis was based on a single transcriptomic dataset with a relatively modest sample size, which may limit the generalizability of the identified signatures. Second, gene expression was measured in peripheral whole blood rather than ischemic brain tissue, and the observed transcriptional alterations may therefore reflect systemic responses as well as processes directly related to cerebral injury. Third, transcriptomic data alone cannot determine whether changes in gene expression correspond to altered protein abundance, respiratory-chain activity, ATP production, or other measures of mitochondrial function. The observational nature of the analysis also precludes causal interpretation. Finally, the candidate hub genes were identified through computational network analysis and require validation in independent patient cohorts and experimental models (Fu et al., 2026; Z. H. Zhao et al., 2026). Future studies integrating transcriptomic findings with proteomic, metabolomic, and functional mitochondrial measurements may provide a more comprehensive understanding of the contribution of mitochondrial dysfunction to ischemic stroke.

## **CONCLUSION**

This study identified a distinct mitochondria-related transcriptomic signature associated with ischemic stroke, characterized primarily by alterations in genes involved in oxidative phosphorylation, mitochondrial electron transport chain activity, adenosine triphosphate (ATP) metabolism, oxidative stress, and mitochondrial stress responses. Protein–protein interaction (PPI) network analysis identified NDUFA1, NDUFS2, UQCRC1, COX5A, and ATP5F1A as candidate hub genes associated with mitochondrial energy metabolism. These findings provide molecular insights into mitochondria-related transcriptional alterations in ischemic stroke and highlight potential targets for further mechanistic investigation. However, validation using independent clinical datasets and experimental models remains necessary to establish the biological relevance, functional roles, and potential translational significance of the identified mitochondrial signatures.

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## **CONFLICT OF INTEREST**

The authors declare that there are no conflicts of interest related to the conduct of the research, preparation, or publication of this article.

## **AUTHOR CONTRIBUTIONS**

All authors contributed to the preparation of this article. The first author, Ian Pranandi, was responsible for the conceptualization of the study, data collection and analysis, interpretation of the results, and manuscript preparation. The other authors contributed to the review, editing, and final approval of the manuscript.

## GENERATIVE AI STATEMENT

The authors declare that no generative artificial intelligence was used in the preparation of this article.

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