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NETWORK-BASED DISCOVERY OF KEY REGULATORY GENES IN HUNTINGTON'S DISEASE PATHWAYS

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Abstract:

Huntington's disease (HD) is a fatal, inherited neurodegenerative disorder caused by CAG repeat expansion in the HTT gene, leading to progressive motor dysfunction, cognitive decline, and psychiatric symptoms. While the causative mutation is well characterized, the downstream molecular mechanisms driving disease progression remain incompletely understood. In this study, a network-based bioinformatics approach was employed to identify key regulatory genes and pathways involved in Huntington's disease. Disease-associated genes were first retrieved using DisGeNET and subsequently expanded through protein–protein interaction (PPI) analysis using STRING and GeneMANIA. Network visualization and topological analysis were conducted using NetworkAnalyst to identify hub genes based on degree and betweenness centrality. Functional and pathway enrichment analyses were performed using Reactome to uncover biological processes significantly associated with the identified gene network. The integrated analysis revealed several highly connected regulatory genes, including HTT, BDNF, IL6, PPARGC1A, SIRT1, NRF1, and glutamatergic receptor genes (GRIN2A, GRIN2B), implicating mitochondrial dysfunction, neuroinflammation, synaptic signaling, and metabolic dysregulation as central pathways in Huntington's disease pathology. This study demonstrates the utility of network-based systems biology approaches in elucidating complex disease mechanisms and identifying potential therapeutic targets in neurodegenerative disorders.

Keywords: *Huntington disease, HTT, Network Analysis, Ppi.*

Introduction

Huntington's Disease (HD) stands as one of the most rigorously studied yet remains one of the most devastating autosomal dominant neurodegenerative disorders in human clinical genetics. Characterized by a triad of motor dysfunction, psychiatric disturbances, and cognitive decline, the disease is inexorable in its progression, typically leading to death approximately 15 to 20 years following the onset of clinical symptoms. The primary pathology is rooted in the selective and progressive loss of medium spiny projection neurons (MSNs) within the striatum, although the neurodegenerative process eventually encompasses the cerebral cortex and other subcortical structures. While historically viewed through a localized lens focused on the basal ganglia, modern systems biology has revealed that HD is a systemic illness affecting various cellular pathways across the entire organism, including peripheral metabolic and immune functions.[8]

The clinical manifestation of HD, often beginning in mid-adulthood between the ages of 30 and 50, is primarily attributed to the expansion of a CAG trinucleotide repeat within exon 1 of the HTT gene. However, the phenotypic variability observed in the patient population—ranging from juvenile-onset cases with rapid progression to late-onset cases with milder symptoms—suggests that the primary genetic lesion interacts with a complex network of genetic modifiers and environmental factors. This complexity necessitates a departure from traditional reductionist approaches, which focus on isolated genes or proteins, toward a holistic systems biology framework. [20]

Table 1: Clinical Features and Biological Correlations of Huntington's Disease.

Clinical Feature	Description	Biological Correlation
Motor Symptoms	Chorea, dystonia, and motor incoordination	Loss of striatal MSNs and corticostriatal dysregulation
Cognitive Decline	Executive dysfunction and memory impairment	Cortical atrophy and disrupted synaptic plasticity
Psychiatric Deficits	Depression, irritability, and neuropsychiatric changes	Limbic system involvement and neurotransmitter imbalance
Metabolic Changes	Weight loss and altered energy expenditure	Peripheral expression and mitochondrial stress

Note. Data from table adapted from following sources [3,8]

The HTT gene, formerly known as IT15, is a large locus spanning approximately 180 kb on the short arm of chromosome 4. It consists of 67 exons and produces two alternatively polyadenylated transcripts that are widely expressed throughout the body, with the highest concentrations found in the brain and testes. The pathogenic mechanism of HD is fundamentally tied to the unstable expansion of the CAG repeat, which translates into a polyglutamine (polyQ) tract at the N-terminus of the huntingtin protein.[3]

The length of this CAG repeat is the primary determinant of disease onset and penetrance. In the general population, CAG repeat lengths typically range between 6 and 35 repeats, which are considered stable and non-pathogenic. Repeat lengths between 36 and 39 occupy a range of reduced penetrance, where some individuals may develop the disease late in life while others remain asymptomatic. Full penetrance is achieved when the repeat length reaches 40 or more, ensuring the eventual development of the disease in all carriers of the expansion. Notably, repeat lengths exceeding 60 are associated with juvenile-onset HD (JHD), where symptoms

manifest before the age of 20, often characterized by more severe motor and cognitive deficits and a more rapid clinical decline[19]

Table 2: CAG Repeat Length and Clinical Outcomes in Huntington's Disease

CAG Repeat Length	Clinical Classification	Penetrance and Inheritance Implications
6 – 27	Normal	Fully stable; no disease risk
27 – 35	Intermediate	No disease risk; potential for expansion in offspring
36 – 39	Reduced Penetrance	Risk of late-onset HD; incomplete penetrance
40 – 49	Adult Onset	Full penetrance; symptoms typically start at age 30-50
> 60	Juvenile/Childhood Onset	Rapid progression; early mortality

Note. Data from table adapted from following sources [19]

Proteotoxicity and the transition to pathological Huntingtin

The wild-type huntingtin protein (wtHTT) is a massive, 350 kDa molecule primarily composed of alpha-helical HEAT (Huntingtin, Elongation factor 3, protein phosphatase 2A, and TOR1) repeats. These repeats facilitate a vast array of protein-protein interactions, allowing wtHTT to function as a versatile scaffolding hub essential for early embryonic development and neuronal survival. The absence of wtHTT results in embryonic lethality, underscoring its indispensable role in cellular physiology. [3]

Physiologically, wtHTT is involved in numerous cellular processes, most notably axonal transport and transcriptional regulation. It interacts with Huntingtin-Associated Protein 1 (HAP1) and the $p150^{Glued}$ subunit of dynactin to regulate the microtubule-based transport of vesicles, including those containing brain-derived neurotrophic factor (BDNF). Furthermore, wtHTT modulates the transcription of neuron-specific genes by sequestering the Repressor Element 1-Silencing Transcription Factor (REST) in the cytoplasm. This prevents REST from entering the nucleus and binding to the Neuron-Restrictive Silencer Element (NRSE), thereby allowing the expression of BDNF and other critical survival factors.[30]

The expansion of the polyQ tract transforms this beneficial scaffold into a toxic agent (mHTT) through both a gain-of-function and a loss-of-function mechanism. Mutant huntingtin is prone to proteolytic cleavage, often mediated by enzymes like Caspase-6, which generates small, highly aggregate-prone N-terminal fragments. These fragments translocate to the nucleus where they form toxic inclusions and interfere with the transcriptional machinery by sequestering essential transcription factors such as Sp1, CREB, and CBP. Simultaneously, the expanded polyQ tract increases the affinity of mHTT for HAP1, leading to the immobilization of BDNF vesicles and a subsequent loss of neurotrophic support for striatal neurons.[13]

Materials and Methods

Study area

The study area for this research is defined by an in silico computational framework. Data was harvested from global biocuration databases (DisGeNET, OMIM) and processed locally at Pillai College Of Arts Commerce and Science using a Lenovo idea pad 3 workstation. The 'biological site' under investigation is the human molecular interactome, specifically focusing on the regulatory networks associated with Huntington's Disease pathology

Experimental design

The research follows a structured computational pipeline designed to identify key regulatory genes and pathways in Huntington's Disease (HD). This multi-stage approach integrates genomic discovery, protein-network

modeling, and functional validation to provide a comprehensive view of the disease's molecular landscape. Each tool in the workflow was selected for its specific ability to bridge the gap between raw genetic data and clinical relevance, ensuring that the identified "hub genes" are not only mathematically significant but also biologically and medically impactful.

Identification of disease-associated genes using DisGeNET

The initial stage involved the systematic retrieval of disease-associated genes from DisGeNET, a comprehensive discovery platform that integrates information from expert-curated repositories, genome-wide association studies (GWAS), and scientific literature. DisGeNET helps achieve a foundational set of genes by consolidating genotype-phenotype associations from a vast array of high-quality sources, including animal models and human clinical data. By utilizing its sophisticated natural language processing and semantic technologies, the study was able to streamline access to a reliable knowledge base specifically linked to the pathophysiology of HD.

Construction of a protein–protein interaction network using STRING

Once the primary gene list was established, the study transitioned into network construction using STRING (Search Tool for the Retrieval of Interacting Genes/Proteins). This software is designed to map both direct physical and indirect functional protein-protein interactions (PPIs), allowing for the visualization of how these gene products collaborate within a cellular context. STRING helps achieve a system-wide understanding by pooling evidence from experimental assays, computational predictions, and co-expression analysis, resulting in a global network of genome-wide functional connectivity.[22,23]

Network expansion and functional prediction using GeneMANIA

To deepen the biological context, the network was further expanded using GeneMANIA. This tool achieves list extension by identifying functionally similar genes using a "guilt-by-association" approach based on over 800 networks, including co-localization and shared protein domains. It serves to find additional genes that share similar properties with the input list, providing a multi-dimensional view of the genetic landscape by weighting various interaction types to predict gene functions more accurately.[17]

Network topology analysis and hub gene identification using NetworkAnalyst

NetworkAnalyst was employed to perform topological analysis, a process used to identify "hub genes"—those central nodes with high connectivity that likely serve as key regulators within the disease pathway. This tool helps achieve a systems-level interpretation by calculating metrics such as degree and betweenness centrality, which reveal the most influential proteins in a dense interaction network. Its robust visualization framework allows researchers to decompose large networks into functional modules, effectively highlighting the critical bridges of cellular health.[29]

Pathway and functional enrichment analysis using Reactome

To translate mathematical connections into biological insights, Reactome was used for pathway and functional enrichment analysis. As a manually curated and peer-reviewed database, Reactome allows for the mapping of identified genes to specific biological pathways, such as mitochondrial metabolism or synaptic signaling. This helps achieve a clear understanding of how genetic hubs contribute to systematic neurodegeneration by providing expert-reviewed diagrams and structured hierarchies of molecular reactions. [4,6]

Sample collection

Through digital records of a total of 30 high-confidence genes were collected from DisGeNET, which aggregates

clinical and experimental evidence of genotype-phenotype associations for Huntington's Disease.

1. Analytical procedures

1. Network Mapping: Protein-Protein Interaction (PPI) networks were mapped using the **STRING** database. The analytical protocol utilized a probabilistic scoring system, where each interaction is assigned a confidence score based on the strength of supporting evidence (experimental, co-expression, and database mining).
2. Guilt-by-Association Algorithm**: GeneMANIA** was used to extend the network. The analytical procedure involved a linear regression-based algorithm that weights different data sources (e.g., physical interactions vs. co-localization) to predict the functional roles of "neighbor" genes.
3. Topological Metric Calculation: **NetworkAnalyst** was used to perform a quantitative analysis of the network's architecture. Two primary protocols were used:
    - **Degree Centrality:** Counting the number of direct connections per node to identify highly active hubs.
    - **Betweenness Centrality:** Measuring how often a node acts as a bridge along the shortest path between other nodes to identify "bottleneck" proteins.

Statistical analysis

P-value and multiple testing correction:

- P-value: A threshold of $p < 0.05$ was set as the limit for statistical significance.
- FDR (False Discovery Rate): Because bioinformatics involves testing thousands of pathways at once, the Benjamini-Hochberg procedure was used to calculate the Adjusted P-value (FDR). Only pathways with an FDR < 0.05 were considered robust.

Software and Computation: All statistical calculations and network visualizations were generated using:

- **STRING v12.0** (Fisher's Exact Test for enrichment).
- **NetworkAnalyst 3.0** (Topological statistics).
- **Reactome v84** (Binomial test for pathway probabilities).
- **GeneMANIA**

Results

Disease–gene associations identified using DisGeNET

The DisGeNET database was utilized to identify genes associated with Huntington's disease (HD) based on curated literature, experimental evidence, and computational inference. As expected, HTT emerged as the central disease-causing gene. In addition to HTT, several genes implicated in neuronal survival, synaptic transmission, metabolic regulation, and neuroinflammation were identified. Notable genes included BDNF[30], IL6, PPARGC1A, SIRT1[12], GRIN2A, GRIN2B, HAP1[24], and PRNP. These genes formed the foundational seed list for downstream network construction. The diversity of functional roles among these genes suggests that Huntington's disease pathology extends beyond a single molecular pathway and involves coordinated dysregulation across multiple biological processes.

gene_symbol	geneDescription
HTT	huntingtin
HAP1	huntingtin associated protein 1
BDNF	brain derived neurotrophic factor
PPARGC1A	PPARG coactivator 1 alpha
IGF1	insulin like growth factor 1
IL6	interleukin 6
JPH3	junctophilin 3
SIRT1	sirtuin 1
GRIN2B	glutamate ionotropic receptor NMDA type sub
HSF1	heat shock transcription factor 1
CNTF	ciliary neurotrophic factor
NPY	neuropeptide Y
CNR1	cannabinoid receptor 1
GLUL	glutamate-ammonia ligase
PRNP	prion protein (Kanno blood group)
SLC2A3	solute carrier family 2 member 3
ABAT	4-aminobutyrate aminotransferase
NRF1	nuclear respiratory factor 1
PRKAA1	protein kinase AMP-activated catalytic subuni
TFAM	transcription factor A, mitochondrial
GDNF	glial cell derived neurotrophic factor
GRIK2	glutamate ionotropic receptor kainate type su
GRIN2A	glutamate ionotropic receptor NMDA type sub
MAP3K5	mitogen-activated protein kinase kinase kinas
EIF2AK2	eukaryotic translation initiation factor 2 alpha
MAOB	monoamine oxidase B
FAAH	fatty acid amide hydrolase
IL6R	interleukin 6 receptor
NPY2R	neuropeptide Y receptor Y2
SLC29A1	solute carrier family 29 member 1 (Augustine

Figure 1: List of 30 genes associated with Huntington disease

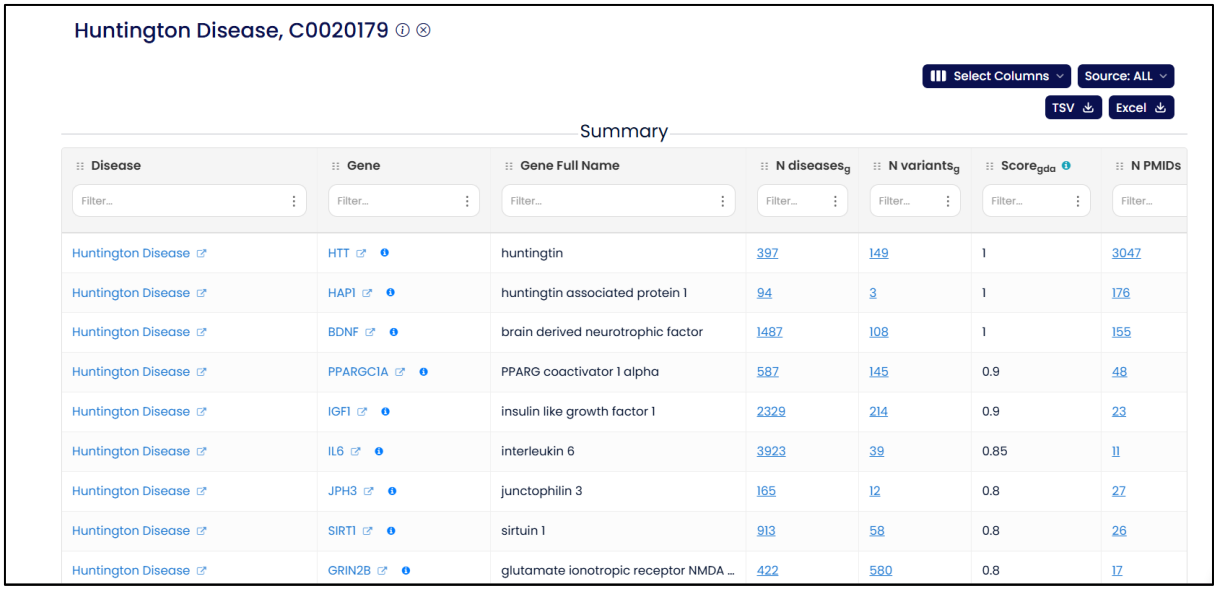

Figure 2: Gene Curation from DisGeNET

Protein–Protein interaction network construction using STRING

Protein–protein interaction (PPI) analysis was performed using the STRING database to explore functional relationships among the identified HD-associated genes. The resulting PPI network revealed a densely interconnected structure, indicating strong functional coupling between disease-related proteins. HTT occupied a central position within the network, interacting directly or indirectly with several key proteins. Neurotrophic factors such as BDNF and GDNF exhibited strong connectivity, highlighting their importance in neuronal maintenance. Similarly, glutamatergic signaling components including GRIN2A and GRIN2B were closely linked, supporting the role of excitotoxicity in HD progression. The PPI network provided a systems level

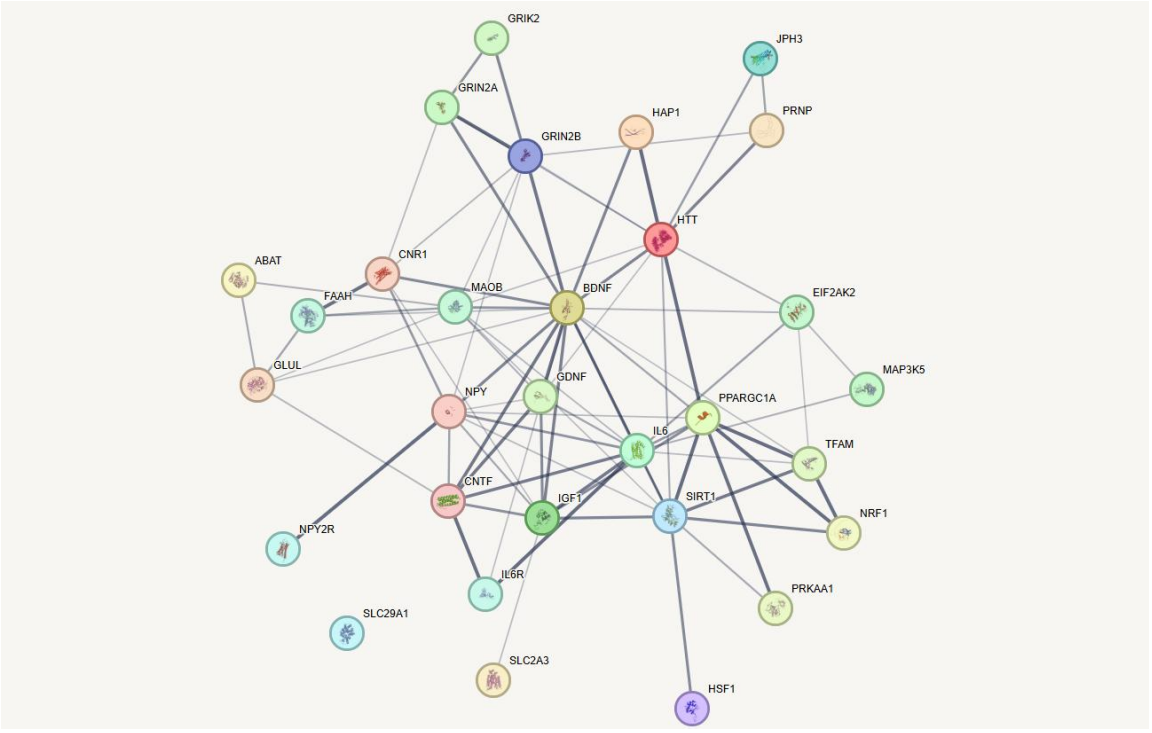

Figure 3: Protein-Protein Interaction (PPI) Network of Huntington's Disease-Associated Genes

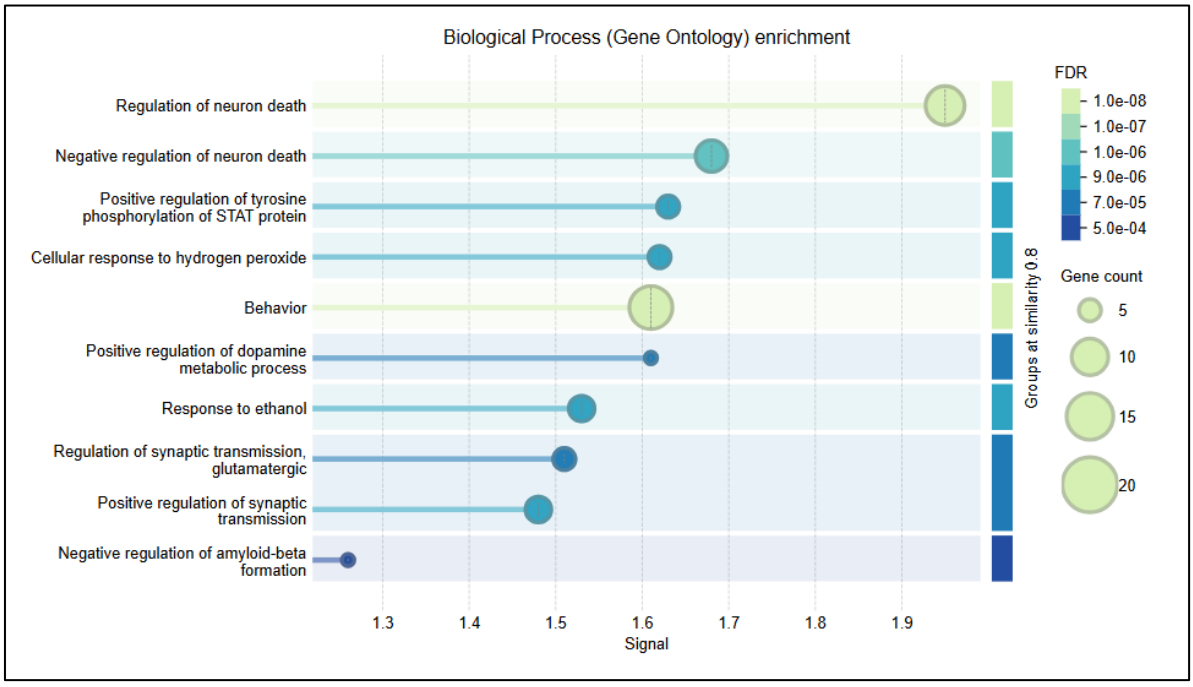

Figure 4: Summary of significantly enriched GO terms and signaling pathways identified from network-based functional analysis of huntington disease

Table 3: Representative GO terms / Pathways from String

Theme	Representative GO terms / Pathways
Neurodevelopment & Structure	Anatomical structure development (GO:0048856), Animal organ development (GO:0048513), Brain development (GO:0007420).
Neuronal Morphology & Localization	Axon (GO:0030424), Cell projection (GO:0042995), Dendrite (GO:0030425), Distal axon (GO:0150034).
Synaptic Signaling & Glutamate Activity	Glutamate-gated calcium ion channel activity (GO:0022849), Ionotropic glutamate receptor activity (GO:0004970).
Cellular Signaling & Homeostasis	Growth factor activity (GO:0008083), Interleukin-6 receptor binding (GO:0005138), Identical protein binding (GO:0042802), Endomembrane system (GO:0012505).

Note. Data from table adapted from String

Network expansion and functional prediction via GeneMANIA

GeneMANIA was employed to expand the initial HD gene set and predict additional functionally related genes. The analysis incorporated multiple evidence types, including physical interactions, co-expression, pathway associations, predicted interactions, co-localization, genetic interactions, and shared protein domains. Physical interactions accounted for approximately 38.13% of the network, while co-expression contributed 20.55%, indicating that both direct molecular interactions and coordinated gene expression patterns play major roles in HD-related networks. GeneMANIA identified additional genes such as IL6ST, CNRIP1, LRPPRC, TFB2M, and NPY1R, which were not part of the initial seed list. Many of these genes are involved mitochondrial regulation, inflammatory signaling, and neuropeptide-mediated communication, suggesting previously underexplored mechanisms contributing to disease pathology.[17]

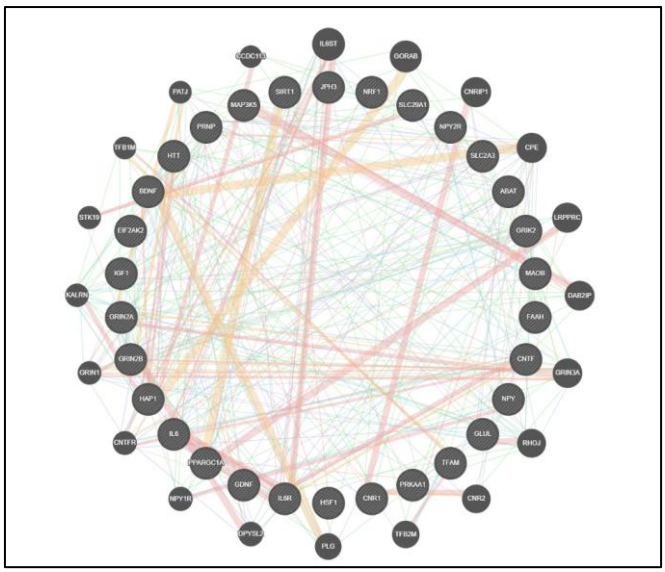

Figure 5: Functional Interaction Map of Identified Hub Genes in Huntington's Disease

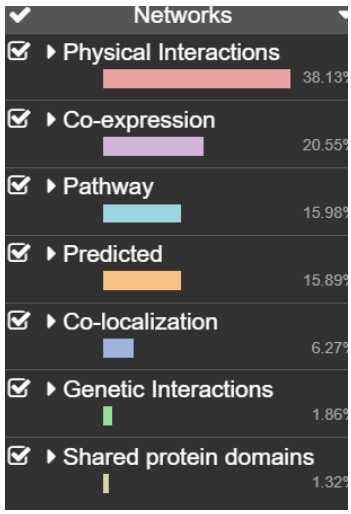

Figure 6: Percentage of networks from Genemania

Network topology and hub gene identification using NetworkAnalyst

To evaluate the topological importance of genes in the Huntington's disease network, degree and betweenness centrality were calculated to identify central hubs and critical bottlenecks. SIRT1 emerged as the primary hub and bottleneck in the network, possessing the highest degree (52) and betweenness centrality (32,986.08), which characterizes it as a master regulator that bridges metabolic stress pathways with neuronal survival. The huntingtin gene (HTT) itself followed as a major structural hub with a degree of 49 and a betweenness of 16,408.84, underscoring its role in coordinating vast protein-protein interaction networks that collapse when the protein is mutated. Energy metabolism and excitotoxicity also appear as central themes in the network topology, represented by PRKAA1 (degree 34, betweenness 15,576.79) and GRIN2B (degree 29, betweenness 5893.75), respectively. Additionally, the presence of PPARGC1A (degree 26, betweenness 8255) as a significant node further validates the disruption of mitochondrial biogenesis and bioenergetics in the disease state. Collectively, these topological metrics suggest that the disease network is highly dependent on a few critical proteins, particularly SIRT1 and HTT.

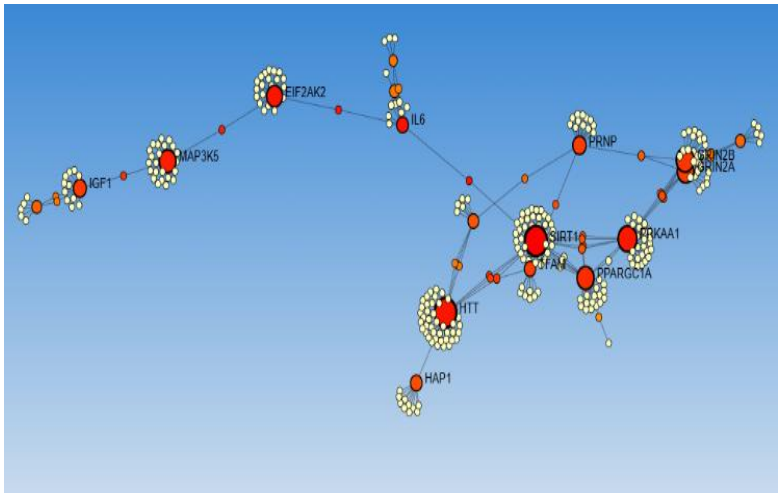

Figure 7: Protein-protein interaction network where the node size and color intensity represent hierarchical importance

Id	Label	Degree	Betweenness	Expressior
23411	SIRT1	52	32986.08	0
3064	HTT	49	16408.84	0
5562	PRKAA1	34	15576.79	0
2904	GRIN2B	29	5893.75	0
10891	PPARGC1A	26	8255	0
4217	MAP3K5	25	12264	0
2903	GRIN2A	25	4699.75	0
5610	EIF2AK2	22	16950	0
5621	PRNP	15	4911.15	0
3479	IGF1	14	5596.5	0
3569	IL6	11	19369	0
9001	HAP1	11	3005	0
7019	TFAM	10	4849.41	0
3297	HSF1	9	2421.14	0
627	BDNF	7	1515.5	0
2898	GRIK2	7	1515.33	0
3570	IL6R	7	914	0
1270	CNTF	5	912	0
7157	TP53	3	5156.44	0
5566	PRKACA	3	2980.12	0

Figure 8: The degree and betweenness measures from network analyst for huntington genes

Pathway and functional enrichment analysis using Reactome

To provide biological context for the identified gene network, pathway enrichment analysis using Reactome revealed a multi-layered disruption of neuronal health. Most statistically robust was the FOXO-mediated transcription of oxidative stress, metabolic, and neuronal genes. To provide biological context for the identified gene network, pathway enrichment analysis using Reactome revealed a multi-layered disruption of neuronal health. Most statistically robust was the FOXO-mediated transcription of oxidative stress, metabolic, and neuronal genes p-value of 4.93E-4 and a False Discovery Rate (FDR) of 6.94E-3, signaling a severe failure in cellular defenses against reactive oxygen species and metabolic instability. This is compounded by evidence of impaired bioenergetics, with genes like PPARGC1A, NRF1, and TFAM enriched in mitochondrial pathways.[4,6]

At the functional level, the Degradation of GABA p-value = 3.65E-2 reflects the progressive loss of striatal medium spiny neurons, which removes the "brakes" on motor signals and leads to chorea. Simultaneously, the Protein-protein interactions at synapses pathway p-value = 3.39E-2 indicates that mutant Huntingtin disrupts synaptic scaffolding, causing communication failure and axonal degeneration. Together, these results signify a systemic collapse where structural synaptic failures, loss of inhibitory signaling, and the breakdown of FOXO-driven "cleanup" systems converge to drive neuronal death.[5]

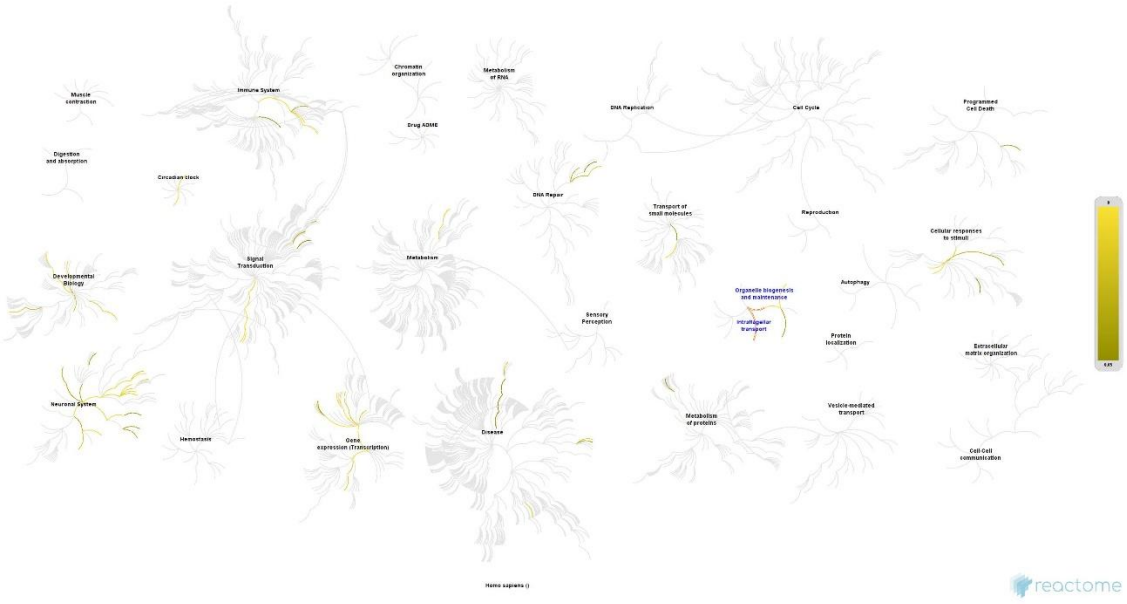

Figure 9: Genome-wide hierarchical map organizes biological processes into functional "bursts" for huntington genes

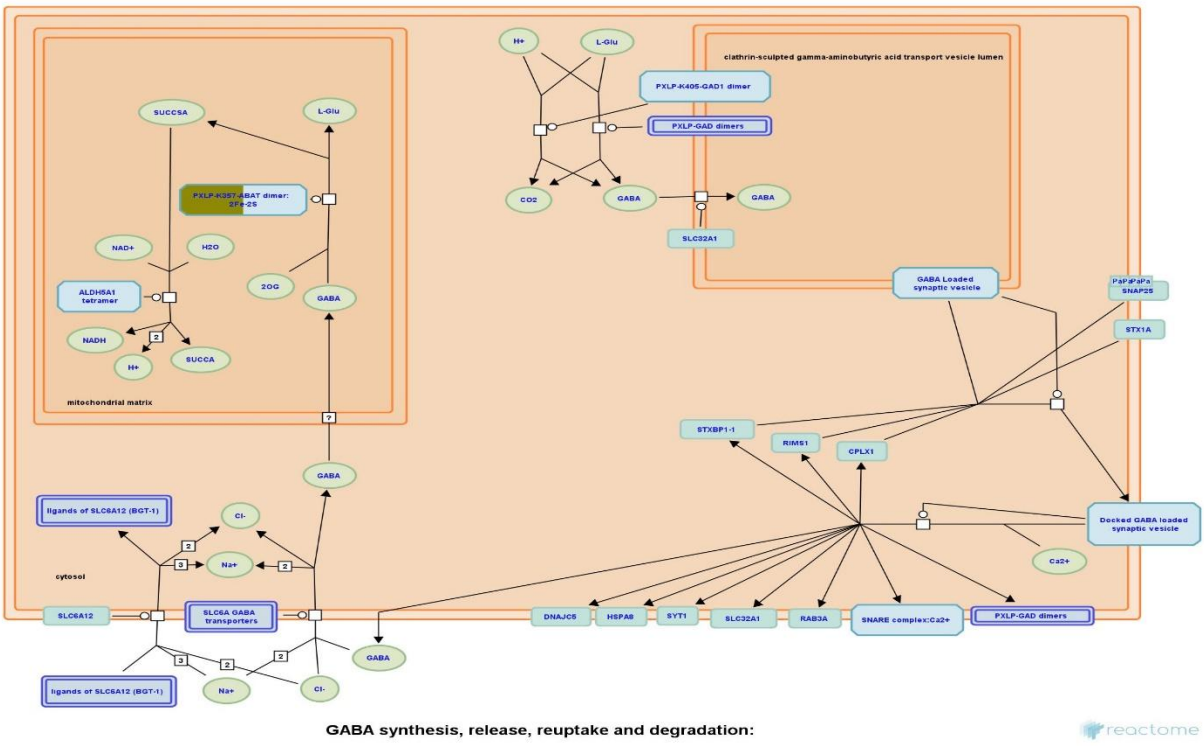

Figure 10: Mechanistic mapping of HT genes within the Reactome "GABA SYNTHESIS AND RELEASE" pathway, integrated with PPI data.

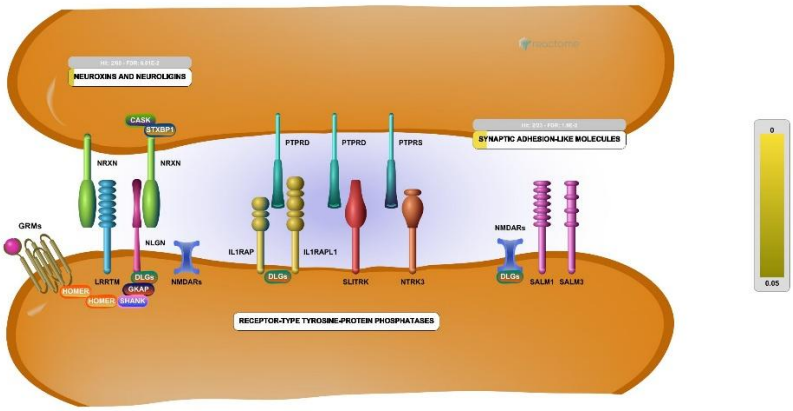

Figure 11: Complex structural landscape of protein-protein interactions at the synapse, highlighting the critical recruitment and organization of adhesion molecules like neuroxins, neuroligins, and synaptic adhesion-like molecules that maintain the physical integrity and signaling efficiency of the synaptic cleft

Discussion

The systems-level analysis of the Huntington's Disease (HD) interactome reveals a complex, multifactorial landscape where genetic mutation translates into systemic cellular failure. By integrating data from DisGeNET, STRING, and Reactome, this study identifies a regulatory core that extends beyond the primary HTT mutation to include critical hubs in metabolism, neuroinflammation, and synaptic integrity. Topological metrics identified SIRT1 as the most significant master regulator and bottleneck within the network, exhibiting the highest degree (52) and betweenness centrality (32,986.08), which characterizes it as a bridge between metabolic stress pathways and neuronal survival. The HTT gene maintains its role as a major structural hub with a degree of 49, suggesting that its mutation leads to a collapse of vast protein-protein interaction networks. Other significant hubs such as PRKAA1 (degree 34) and GRIN2B (degree 29) highlight the network's reliance on energy homeostasis and excitotoxicity management, respectively.

Functional analysis reveals that HD pathology is driven by the convergence of several dysregulated biological processes. The FOXO-mediated transcription of oxidative stress and metabolic genes showed the highest statistical robustness indicating a severe breakdown in cellular defenses and metabolic instability. Simultaneously, the degradation of GABA reflects the progressive loss of striatal medium spiny neurons, providing a molecular explanation for the clinical manifestation of chorea. Enrichment in synaptic scaffolding pathways suggests that mutant Huntingtin disrupts the physical integrity and signaling efficiency of the synaptic cleft, causing communication failure and axonal degeneration. Furthermore, the involvement of PPARGC1A, NRF1, and TFAM validates the disruption of mitochondrial biogenesis and bioenergetics as a central theme in disease progression. While traditional models focus on protein aggregation, this network-based approach emphasizes the role of secondary messengers like IL6 and BDNF, suggesting that neuroinflammation and the loss of neurotrophic support are equally vital to the disease's molecular core.

Conclusion

This study demonstrates that network-based bioinformatics approaches provide powerful insights into the complex molecular landscape of Huntington's disease. By integrating disease–gene associations, protein

interaction networks, functional prediction, and pathway enrichment, key regulatory genes including SIRT1, HTT, PRKAA1, and GRIN2B were identified as primary drivers of HD progression. The findings underscore the interconnected roles of neuroinflammation, mitochondrial dysfunction, and synaptic signaling in disease pathology. From a therapeutic perspective, these network-derived targets could inform the development of multi-target strategies to combat systemic neuronal collapse. However, as this study relies on curated databases and computational predictions, future work should focus on experimental validation using transcriptomic and proteomic data from HD patient samples to further elucidate these progression mechanisms.

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