MICROBIOME meets miRNA: New Regulators of PD & HD

47th ESPEN CONGRESS

NETWORK-BASED INVESTIGATION OF MIRNA AND MICROBIOME INTERACTIONS IN PARKINSON'S AND HUNTINGTON'S DISEASE: A SYSTEMS BIOLOGY APPROACH

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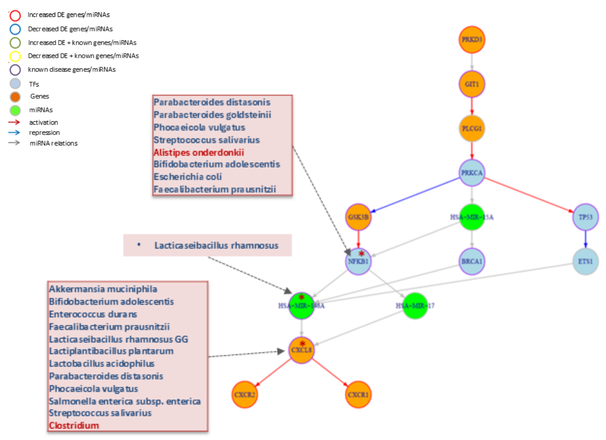
Background

Parkinson's disease (PD) and **Huntington's disease (HD)** are complex neurodegenerative disorders with high societal and clinical burden. Pathogenesis involves both **genetic dysregulation** (transcriptional and post-transcriptional) and **environmental influences**, including the gut microbiome. **miRNAs** act as key post-transcriptional regulators of neuronal homeostasis, synaptic plasticity, and immune responses.

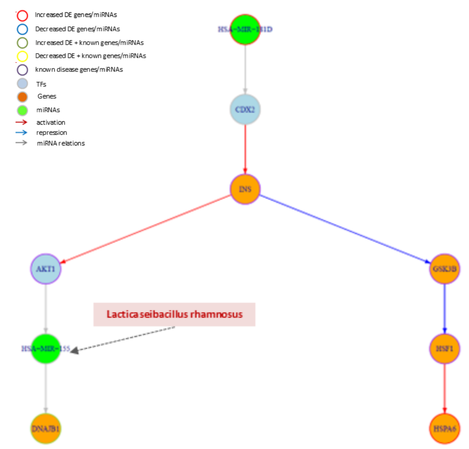
Gut microbiota can modulate host gene expression through immune and metabolic pathways, shaping neuroinflammatory and neurodegenerative processes. Yet, **integrative network-based approaches** that combine miRNA, transcription factor, gene expression, and microbiome–host interactions are scarce. A **systems biology framework** is therefore needed to uncover hidden regulatory modules and novel therapeutic targets.

Results



Result 1:

- **NFKB1** hub is differentially modulated by microbiota:
  Faecalibacterium, Bifidobacterium, Parabacteroides inhibit → anti-inflammatory;
  Alistipes activates → pro-inflammatory.
- **miR-146a**, a negative regulator of NF-κB signaling, is inhibited by *Lacticaseibacillus rhamnosus*, linking microbial signals to loss of immune control in HD.
- **CXCL8 (IL-8)** pathway is broadly inhibited by beneficial taxa (*Akkermansia, Lactobacillus, Faecalibacterium*), but activated by *Clostridium*, suggesting microbial balance dictates neuroinflammatory tone.



Result 2:

- **miR-155**, a pro-inflammatory miRNA regulating NF-κB and apoptosis, is activated by *Lacticaseibacillus rhamnosus*.
  While not differentially expressed in PD data, its presence in the integrated network suggests a potential novel PD-related regulator.
- **CDX2**, a master regulator of intestinal epithelial genes, connects to **INS** → **AKT1/GSK3B**.
  Although not validated in PD datasets, its appearance in the PD network highlights a possible gut–metabolic–inflammatory link to PD.
- IBD patients show increased PD risk, while anti-TNF therapy reduces PD incidence, supporting the hypothesis that intestinal inflammation and NF-κB/miR-155 signaling contribute to PD.

Method

Step 1: Directed PPI Regulatory Network Construction
SIGNOR (SIGnaling Network Open Resource)
Interactions: 12447 | Nodes: 4731

Step 2: Extension of Directed PPI Network

Databases	Main Feature
TransmiR	the experimentally validated **TF-microRNA** interactions database
miRTarBase	the experimentally validated **microRNA-target** interactions database
miRecords	manually curated database of experimentally validated **miRNA-target** interactions
TarBase	manually curated collection of experimentally tested **miRNA - targets**

Databases	Main Feature
TRANSFAC	the database of eukaryotic transcription factors
TRED	a transcriptional regulatory element database

Databases	Main Feature
HMDD (the Human microRNA Disease Database)	a database of curated experiment-supported evidence for human microRNA (miRNA)
miR2Disease	a manually curated database, aims at providing a comprehensive resource of miRNA deregulation in various human diseases

Step 3: Disease Related Regulatory Network Construction

Prefrontal Cortex Samples: **26** HD patients, **49** neurologically normal control; **29** PD patients, **33** neurologically normal control

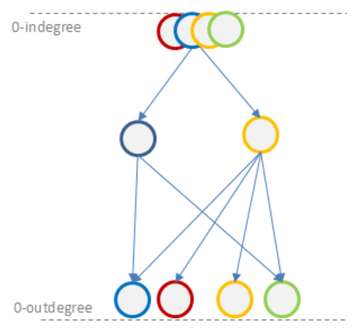
	Huntington Disease (HD)	Parkinson Disease (PD)
RNA-seq Gene Expression Data	GSE64810	GSE68719
miRNA Expression Data	GSE64977	GSE72962

Huntington's Disease	DE miRNAs	DE genes
increased expression	26	165
decreased expression	16	17

Parkinson's Disease	DE miRNAs	DE genes
increased expression	31	11
decreased expression	33	1

Step 4: Subnetwork Construction
3rd degree neighbors of nodes → **Subgraph: 4474/14605**

Step 5: Discovering Important Regulatory Pathways



- Root and Leaf nodes are determined
- All directed acyclic pathways are identified
  →Shortest path algorithm
- CR-value (coverage rate) is calculated

$$CR = \frac{ND}{NT}$$

ND: #of disease related known nodes
NT: length of the path

- **Louvain clustering** to detect functional modules
- FDR-value < 0.2 → important regulatory pathways

Summary/ Highlights

- In HD, the **TP53–ETS1–miR-146a axis** and **CXCL8–CXCR1/2 signaling** highlight neuroinflammation and demyelination as key processes. Microbiome taxa differentially modulating these nodes suggest that **gut–immune interactions** may represent a clinically relevant bridge to HD pathology.
- **miR-155** and **CDX2** may represent **novel PD-related regulatory elements**, linking microbiome signals (e.g., *Lacticaseibacillus rhamnosus* for miR-155, intestinal regulation for CDX2) to NF-κB/apoptosis and metabolic cascades.
- Patients with **inflammatory bowel disease (IBD)** show increased PD risk, while **anti-TNF therapy** reduces PD incidence by ~78%, supporting a mechanistic bridge between intestinal inflammation, NF-κB/miR-155 signaling, and PD.

SCAN ME!

References

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47th ESPEN CONGRESS

47th ESPEN Congress
on Clinical Nutrition & Metabolism
Prague, Czech Republic
13-16 September 2025
Prague Congress Center