Lesch-Nyhan Syndrome (LNS) and the HPRT1 Gene

Billy Maes
What is Lesch-Nyhan Syndrome?

- Gouty arthritis
- Kidney stones
- Loss of motor control
- Cognitive problems
- Self-mutilation
What is Lesch-Nyhan Syndrome?

https://youtu.be/1U6LDpF_LFE?t=58s
What causes Lesch-Nyhan Syndrome?

**Unknown mechanism → neurological symptoms**

Excess uric acid → gout and kidney stones
>300 mutations in *HPRT1* are known to cause LNS

Point mutations
Loss-of-function mutations
Change in size, shape

Phosphoribosyltransferase domain
218 aa

HPRT protein
How well conserved is HPRT?

<table>
<thead>
<tr>
<th>Species</th>
<th>Phosphoribosyl transferase domain</th>
<th>% Identity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>218 aa</td>
<td>97%</td>
</tr>
<tr>
<td>Mouse</td>
<td>218</td>
<td>97%</td>
</tr>
<tr>
<td>Chicken</td>
<td>218</td>
<td>91%</td>
</tr>
<tr>
<td>Zebrafish</td>
<td>218</td>
<td>91%</td>
</tr>
<tr>
<td>Roundworm</td>
<td>214</td>
<td>49%</td>
</tr>
<tr>
<td>Arabidopsis</td>
<td>188</td>
<td>31%</td>
</tr>
</tbody>
</table>
What are HPRT1’s GO terms?

**Biological Processes**
- Neuron development and differentiation
- Purine Salvage Pathway
- Dopamine metabolism
- Dendrite morphogenesis
- Locomotory behavior

**Molecular Functions**
- Nucleotide binding
- Phosphoribosyltransferase activity
- Magnesium ion binding

**Cellular Components**
- Cytoplasm

**Dopamine Pathways**
- Frontal Cortex
- Nucleus Accumbens
- Striatum
- Hippocampus

Functions
- Reward Motivation
- Motor Function
- Compulsion
Dopamine

Pleasure
Reward motivation
Motor function
Compulsive behavior

Pharmacological Rat Model
Reduce brain dopamine in neonatal rats using neurotoxin 6-OHDA

**LNS phenotypes may be caused by abnormal brain development, induced by low dopamine levels neonatally**
Gap in Knowledge
Hypothesis

**Hypothesis:** *HPRT1* regulates the development of the dopaminergic system, important for normal cognition and behavior, through protein interactions in the brain.
Primary Goal: Determine the genomic and proteomic changes that contribute to LNS neurological dysfunction as a result of loss-of-function mutations in HPRT1.
Zebrafish: A Model Organism for LNS

91% identity to human HPRT

Phosphoribosyl transferase domain

218 aa
Specific Aim #1: HPRT interaction partners

Affinity purification- mass spectrometry (AP-MS)

STRING database

Determine function of HPRT interaction partners
Specific Aim #1: HPRT interaction partners

**Hypothesis: SQSTM1 activates NF-KB (synaptic plasticity & dendrite growth), NGF (nerve growth), and titin/TTN (linked to movement disorders)**
Specific Aim #2: Altered Protein levels?

Quantitative mass spectrometry: Compare protein levels in wild-type and HPRT-mutant zebrafish

**Hypothesis: SQSTM1 decreases in HPRT mutants**
Specific Aim #3: Altered gene expression during brain development?

**This will indicate when mutations in \textit{HPRT1} alter neuronal gene function, indicating how brain development may be altered.**
Conclusions

Aims: indicate how gene expression and protein interactions change as a result of HPRT mutations.

Gain insight into the mechanisms that lead to the neuronal-behavioral phenotypes of LNS.

Future Directions

Alter levels of SQSTM1 and other proteins that interact with HPRT1. Observe if neurological or behavioral LNS phenotypes appear in mice.