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Exploring the Genetic Basis of Cognition and Anxiety Through the Human Lynx Genes: The SNP Project

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Exploring the Genetic Basis of Cognition and Anxiety Through the Human Lynx Genes: The SNP Project

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Dr. Julie Miwa, Principal Investigator

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Brain & Lynx 2

- Lynx2
  - Expressed in the amygdala
  - Regulates fear and emotion
Receptor Binding

lynx1
Mouse Experiments

*lynx2* KO mice are more:

- anxious (Tekinay et al., 2006)
- antisocial (Tekinay et al., 2006)

![Light-Dark Box Experiment](image)
Limitations of mouse studies

• Performed in mice, not humans
  ◦ Could be applicable to:
    ◦ Neurodegenerative diseases
    ◦ Mental disorders
    ◦ Normal differences in cognition and personality

• Studied unnatural genetic variation
  ◦ Genetic engineering- KO mice
Natural Variation- Single Nucleotide Polymorphisms (SNPs)

• Nucleotide- the building block of DNA

• Four different nucleotides: A, T, G, C
Why do SNPs matter?
Why do SNPs matter?
The SNP Project

• Explore the presence and effect of SNPs in the human lynx genes on the lynx proteins and behavior

• Goal: To correlate single nucleotide polymorphisms (SNPs) in the lynx2 gene with variation in anxiety behaviors

• Develop lynx genes into novel treatments for related pathologies

• Integration of neuroscience, genetics, proteomics, bioinformatics and cognitive psychology
Hypothesis

- SNPs causing decrease in expression of the *lynx* genes or decreased binding affinity of the *lynx* proteins =

- SNPs causing increase in expression of *lynx* genes or increased binding affinity of the *lynx* proteins =
# Project Overview and Progress

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<th>Bioinformatics</th>
<th>Psychology</th>
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Gene Schematic and Primer Design - lynx2

Exon 3 Primer Region

Exon 4 Primer Region

Transcription Start Site
Exon
Signal Sequence

Translation Start Site
Mature Protein Coding Sequence
GPI Anchor Signal Sequence

Translation Stop Site
Intron
Region amplified by a primer
Data Collection

• Have run ~456 participants
  o ~44 Summer 2015
  o ~43 Fall 2015
  o ~67 Spring 2016
  o ~50 Summer 2016
  o ~156 Fall 2016
  o ~96 Spring 2017

• Testing
  o Biology Core Classes
  o Started collecting at NCC
Preliminary Results: lynx2

- Found 8 SNPs, all in protein region
- One may cause a functional KO
### Summary of confirmed GenBank SNPs

<table>
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<th>SNP</th>
<th>Frequency</th>
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<tr>
<td>K47I</td>
<td>0.00002480</td>
</tr>
<tr>
<td>C6*</td>
<td>0.00001654</td>
</tr>
<tr>
<td>M31V†</td>
<td>0.00000827</td>
</tr>
<tr>
<td>V22Q†</td>
<td>0.00000826</td>
</tr>
<tr>
<td>M(1)V†</td>
<td>0.00000827</td>
</tr>
<tr>
<td>Q29*†</td>
<td>0.00000827</td>
</tr>
</tbody>
</table>

- Data from McLaughlin et al., submitted manuscript
- **We are currently analyzing a mutation that occurs in humans at a 4% rate.**

†Protein is not validated in NCBI's database. However, it does have frequency data, which means that this sequence was submitted multiple times and is a form of validation in itself.
Predicted structure of mutated *lynx2* proteins

- *lynx2* wild type
- *lynx2* SNP 101
  - amino acid 47 frameshift
- *lynx2* polypeptide
  - amino acid 1 frameshift

*This SNP was found in our participant samples.*
Next Steps

Summer Mountaintop Project 2017
Score tests and correlate SNPs to different behavioral differences
Co-model mutated *lynx* proteins with nicotinic acetylcholine receptors/ create mutated *lynx* proteins for electrophysiology and behavioral experiments
Thank you, Questions?