5-1-2017

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

Sana Ali, Undergraduate SNP Project Co-Leader & Eckardt Scholar

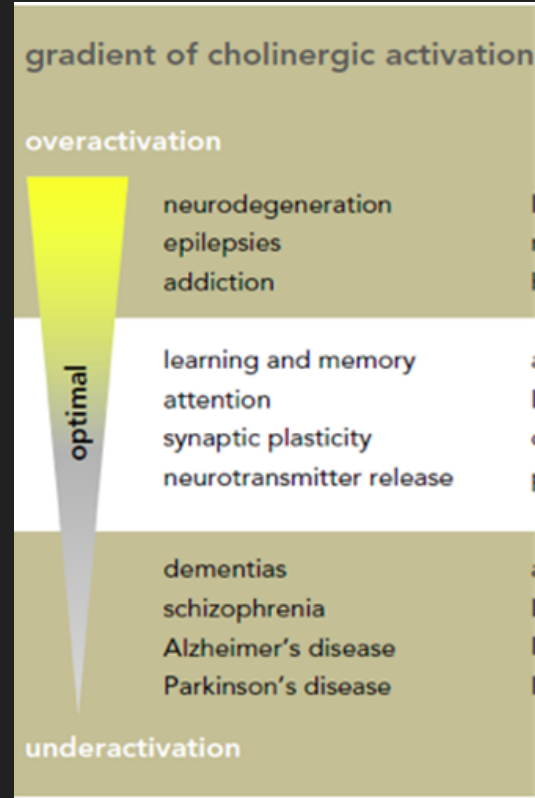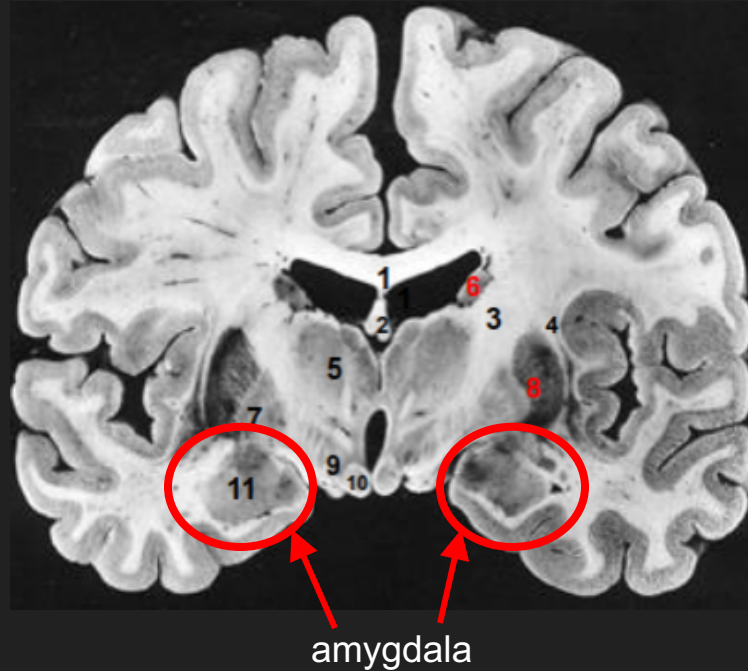**Kristin Anderson, Lead Graduate Student and Trainer**

Dr. Julie Miwa, Principal Investigator

Other important researchers: Reem Azar, Assistant Undergraduate SNP Project Co-Leader, Kyra Feuer, Amanda DeGraaf, Brian Pezzuti, Rohil Parikh, Vikram Muller, Morgan Decker, Christopher Hoke, Andrew Truman, Edwin Chan, Simon Voorhees, Crystal Lovelace, Spring 2015 Bios 296 class, Fall 2015 Bios 296 Class, Ben Davis, Trishna Dave, Maggie Dalena, Sneha Alaparhi, Sonja Gorman, Haley Lombardo, Dr. Krystle McLaughlin, Dr. Almut Hupbach, Dr. Nancy Wayne
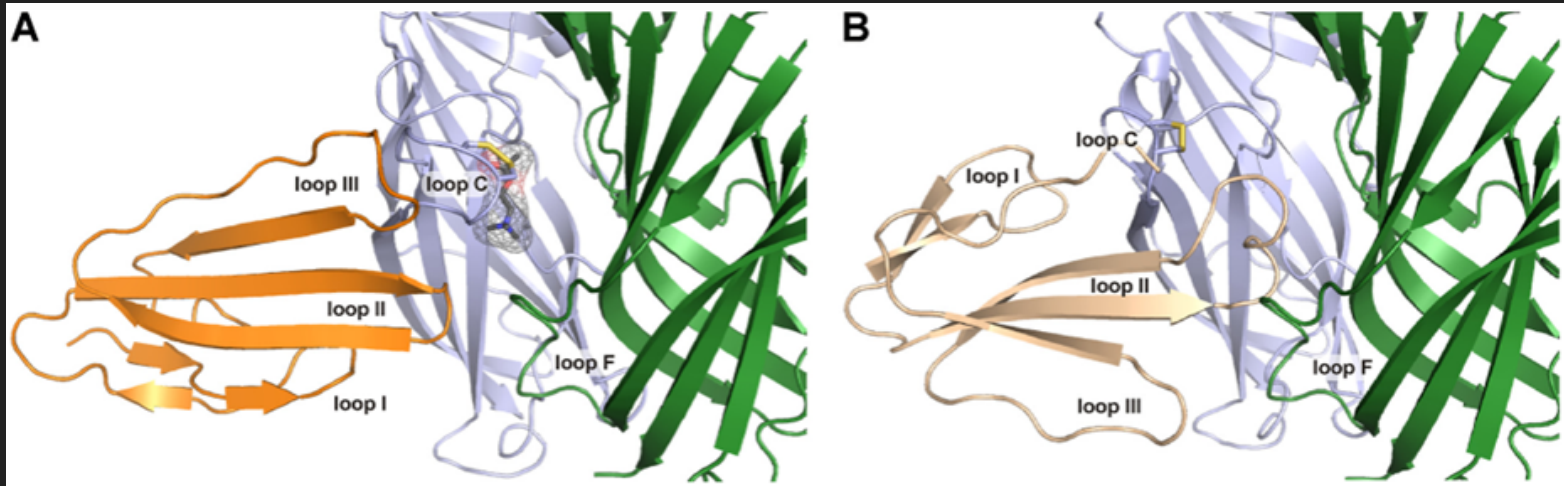
Brain & Lynx 2

- *Lynx2*
  - Expressed in the amygdala
  - Regulates fear and emotion

amygdala

gradient of cholinergic activation

overactivation

neurodegeneration
epilepsies
addiction

optimal

learning and memory
attention
synaptic plasticity
neurotransmitter release

dementias
schizophrenia
Alzheimer's disease
Parkinson's disease

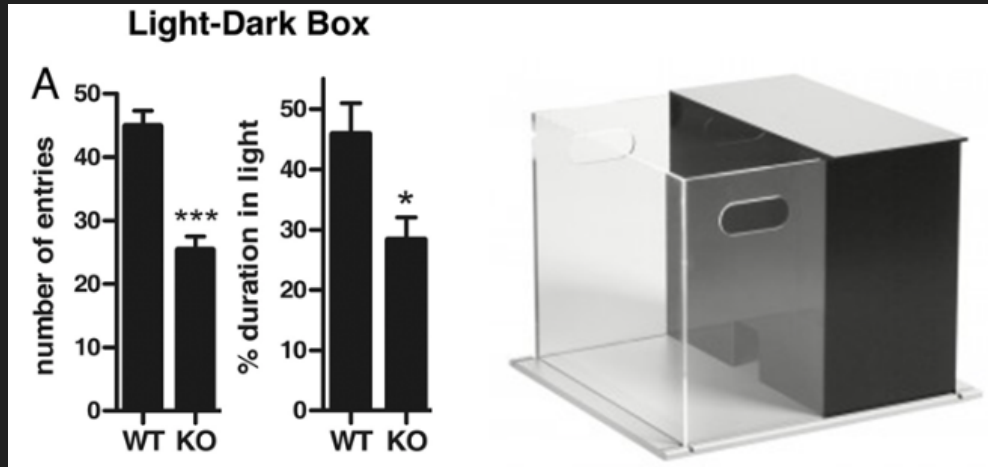underactivation

Receptor Binding

lynx1

Mouse Experiments

lynx2 KO mice are more:

- anxious (Tekinay et al., 2006)

- antisocial (Tekinay et al., 2006)

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

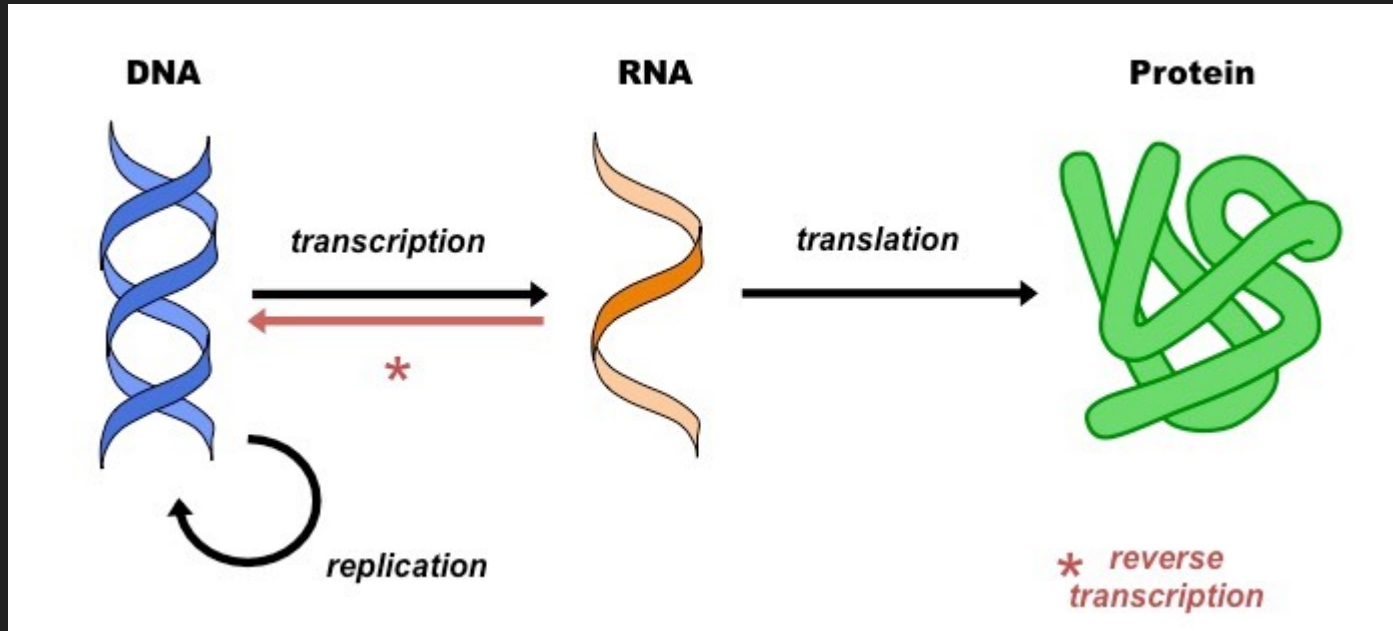# Natural Variation- Single Nucleotide Polymorphisms (SNPs)

- Nucleotide- the building block of DNA

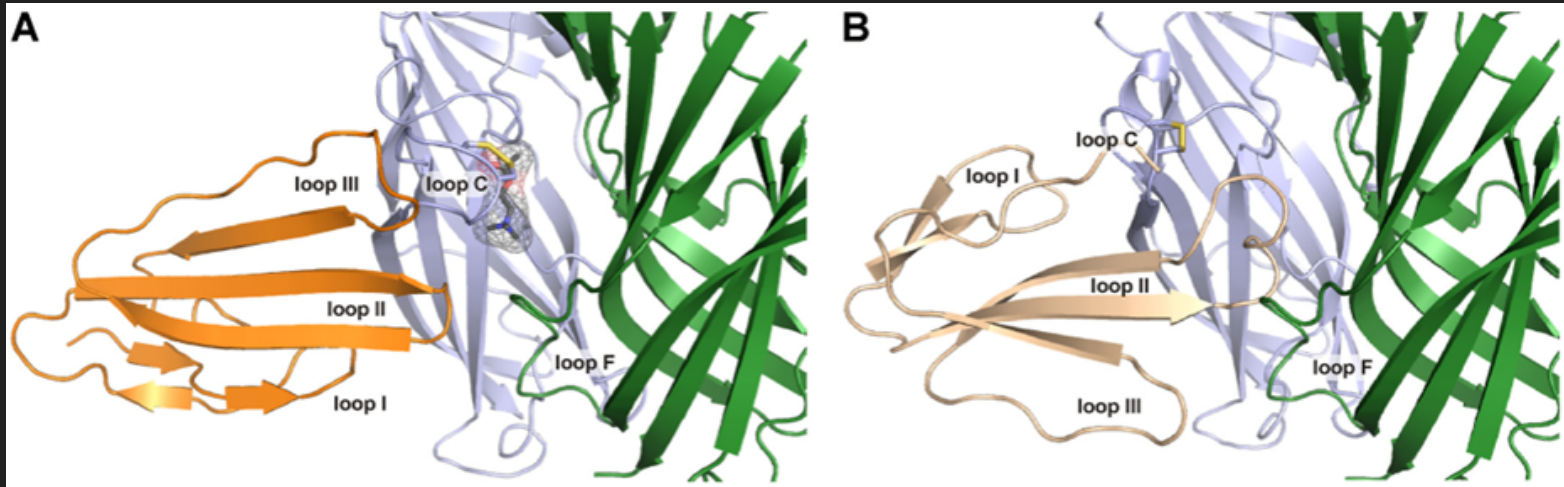- Four different nucleotides: A, T, G, C
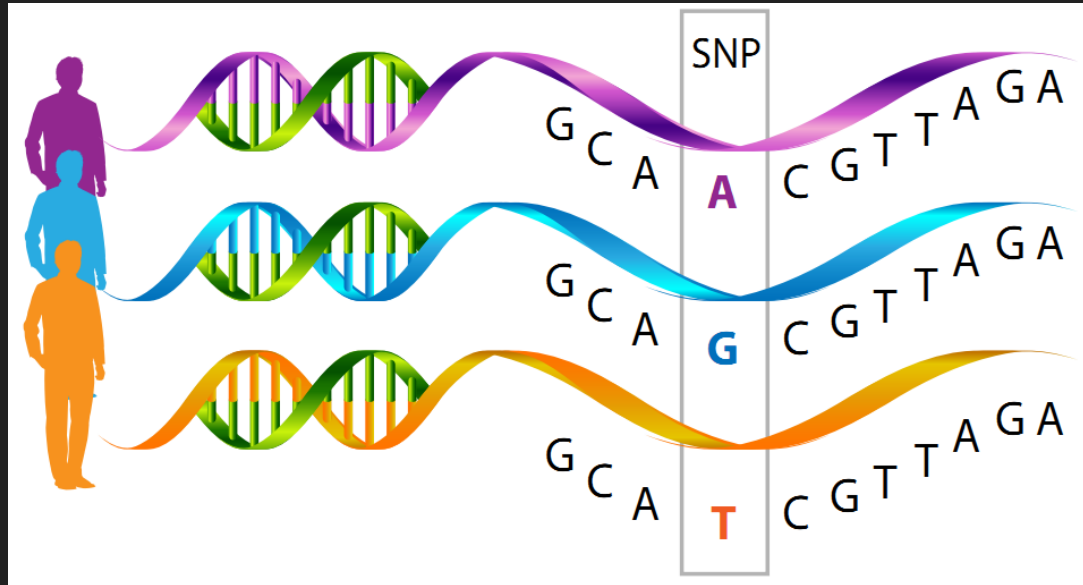
Why do SNPs matter?

Why do SNPs matter?

lynx1

The SNP Project
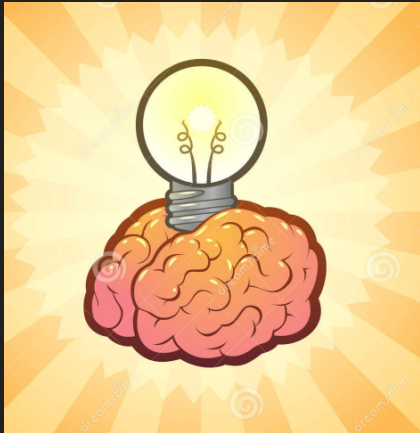
- Explore the presence and effect of SNPs in the **human** *lynx* genes on the *lynx* proteins and behavior

- 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 =
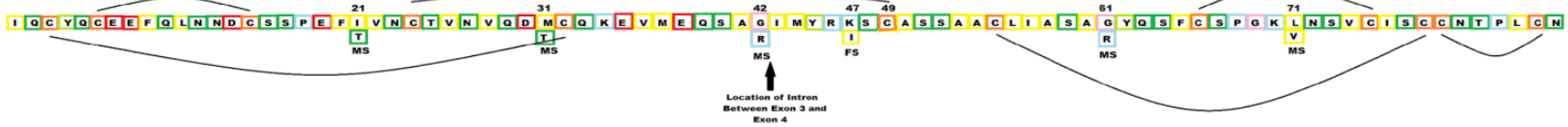
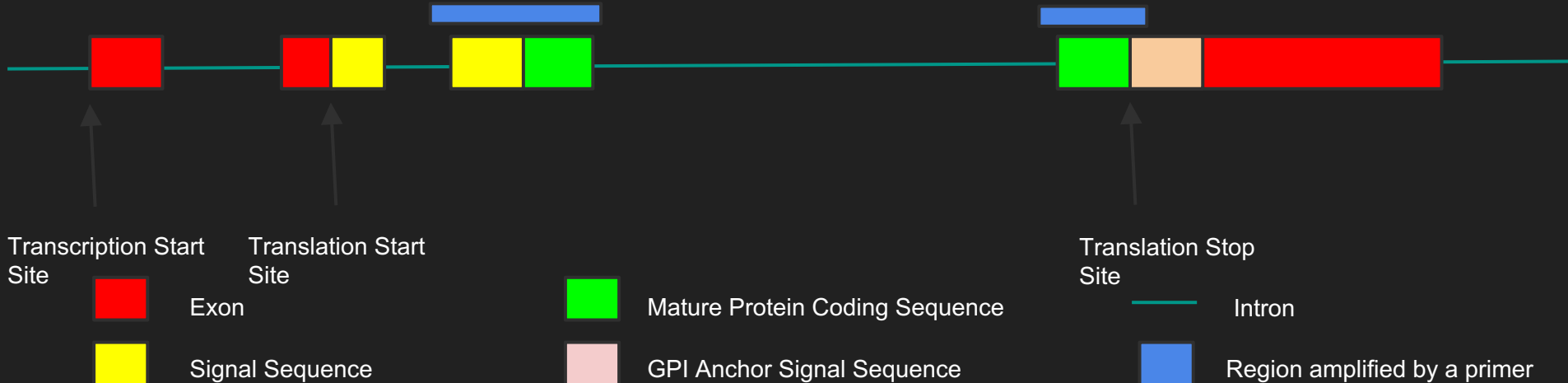# Project Overview and Progress

Wet Lab	Bioinformatics	Psychology
• DNA extraction • PCR &Gel • Gene Sequencing • Isolation of SNPs • Correlation of SNPs to Psych Tests	• PCR design • DNA sequence analysis • Protein Modeling • Neural Net	• Recruitment • Administering tests • Recoding tests • Scoring tests

Gene Schematic and Primer Design- *lynx2*

Exon 3 Primer Region

Exon 4 Primer Region

Transcription Start Site

Translation Start Site

Translation Stop Site

Exon

Signal Sequence

Mature Protein Coding Sequence

GPI Anchor Signal Sequence

Intron

Region amplified by a primer

Data Collection

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

- Testing
  - Biology Core Classes
  - 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

SNP	Frequency
K47I	0.00002480
C6*	0.00001654
M31V†	0.00000827
V22Q†	0.00000826
M(1)V†	0.00000827
Q29*†	0.00000827

- 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.

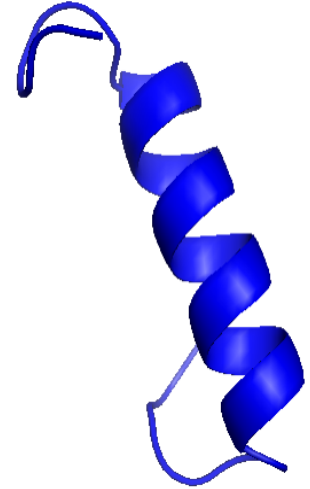# Predicted structure of mutated *lynx2* proteins

lynx2 wild type

lynx2 SNP 101*

lynx2 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?